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INFRACLAVICULAR TUBERCULOUS INFILTRATIONS[1,2]

MAURICE FISHBERG

The dictum, which has become a dogma, that pulmonary tuberculosis almost invariably begins at the apex and that if we are to detect the disease in its earliest stage we must look for changes in that part of the lung, has been rudely shattered of late. To be sure, in most cases of pulmonary tuberculosis the findings obtained at the first examination indicate clearly an apical lesion, but it appears that patients with physical and roentgenological signs of changes in the apices have usually already progressed beyond the stage that can be called "incipient," or have sclerotic lesions which are of little clinical significance. We have learned of late that the earliest active and progressive lesion, the kind that needs treatment, is in the majority of cases found in parts of the lung below the clavicle.

The patient with a real apical lesion is well known to clinicians. He usually has a history of long duration, of colds, cough, at times haemoptysis, and now and then attacks of slight fever and night-sweats which last several days or weeks, but he recuperates with or without treatment every time. In some of these cases tubercle bacilli are detected in the sputum, which, however, is not a constant or frequent phenomenon. We usually elicit that at one time positive sputum was found. The physical signs are those considered sufficient for localization of a lesion in one of the apices, provided there are also haemoptysis and, above all, tubercle bacilli in the sputum; otherwise an experienced clinician may say that the short note obtained on percussion of the apex, the bronchovesicular or feeble breath-sounds, and even the crepitations audible on auscultation are compatible with excellent health. The roentgenological appearance of the apex in which the lesion is located is also well known: dense opacity is seen in one or both supraclavicular regions, most commonly of the ground-glass appearance, or striated shadows may be noted on close inspection. The intercostal spaces may be found narrowed, compared with the opposite unaffected side, indicating old lesions resulting

[1] From the Montefiore Hospital and the Bedford Hills Sanatorium.
[2] Read before the New York Academy of Medicine, October 18, 1927.

in shrinkage. These patients are treated for tuberculosis very successfully; they are the preferred class of "incipients," or early cases said to be the most suitable for sanatorium treatment. But it is noteworthy that they remain "early" cases for many years; even several admissions to sanatoria in various climatic regions do not disqualify them from remaining "incipients." However, it appears that these apical lesions are only rarely the forerunners of chronic phthisis in which the pathological changes spread downward in the lungs, and eventually involve extrathoracic organs, such as the larynx, intestines, etc., leading to a fatal termination sooner or later. In other words, patients harboring these apical lesions only rarely die from tuberculosis. Apical lesions, which hardly ever show tendencies to progression, are also found in patients with extrathoracic tuberculous foci, as in the joints, genitourinary tract, etc., and it is well known that these patients hardly ever develop chronic progressive lung lesions; their culminating disease, if tuberculous, is acute miliary tuberculosis or acute pneumonic phthisis.

For many years clinicians have made strenuous efforts to separate these cases of apical tuberculosis with good prognosis from the clinical forms in which drastic treatment is imperative. Neisser (1) described them as "tuberculosoid;" French authors considered them chronic apical pleurisy, *pleurite apical à répétition* (Piéry (2), Sergent (3)), an idea first suggested by Leaming (4), who taught that the crepitant râles heard over the apex in incipient tuberculosis are altogether friction sounds, produced by rubbing of the two pleural surfaces covered with tubercles. The syndrome described by Krönig (5) as "collapse induration" is apparently of this genre, and I may add that the conception of abortive tuberculosis (6) is evidently supported by the frequency of this sort of apical lesion. It appears that real apical tuberculosis is the least dangerous. Redeker (7) states that, in a practice extending over many years, amply employing the roentgen rays, he had never seen a progressive and fatal case of phthisis following one of these apical lesions. Bräuning (8) collated statistics in support of this very contention, and more recently Romberg (9) has confirmed these observations.

Recent clinical observations tend to show that *in active pulmonary tuberculosis the first or initial lesions appear in most cases in the region of the lung below the clavicle*, most commonly in the upper lobe, but at times in the middle or lower lobe, and that these lesions are not of the indurative type just mentioned as characteristic of apical involvement, but of the exudative, bronchopneumonic and finally caseous types. Heretofore we

knew little or nothing about these lesions because it is difficult, in most cases impossible, to discern them with the clinical methods at our command. Physical signs are almost entirely lacking, and in the very beginning the constitutional symptoms may be very mild, hardly inconveniencing the patient for a long time. In fact, it may be stated that without the aid of the roentgen rays it is practically impossible to detect and to localize these lesions, which are the earliest in active and progressive pulmonary tuberculosis.

The first to publish observations on these infraclavicular lesions was Assmann[3] (9). While examining young men, mainly young physicians, medical students and workers in bacteriological and pathological laboratories, who presented vague symptoms suggestive of tuberculosis but in whom no physical signs could be elicited to localize the lesions, he found that a good roentgenograph often revealed an isolated infiltration located below the clavicle, most commonly in the second or third interspace and toward the periphery of the pulmonic field. In the short time since the appearance of Assmann's first communication many others, notably Redeker (7), Lydtin (10), Dietl (11), Ulrici (12), Warnecke (13), Romberg (8), Staub (14), Klingenstein (15), Dorendorf (16), and Unverricht (17), have confirmed his observation and emphasized their immense bearings on the pathogenesis, pathology, diagnosis and prophylaxis of pulmonary tuberculosis.

The failure of the general practitioner to recognize many early cases of active tuberculosis, and of specialists who fail more often than is generally appreciated, has a reasonable basis. The fact is that it is not possible to elicit reliable physical signs while exploring a chest harboring a very early tuberculous infiltration in the pulmonary parenchyma and the lesion may lurk for months without pronounced constitutional symp-

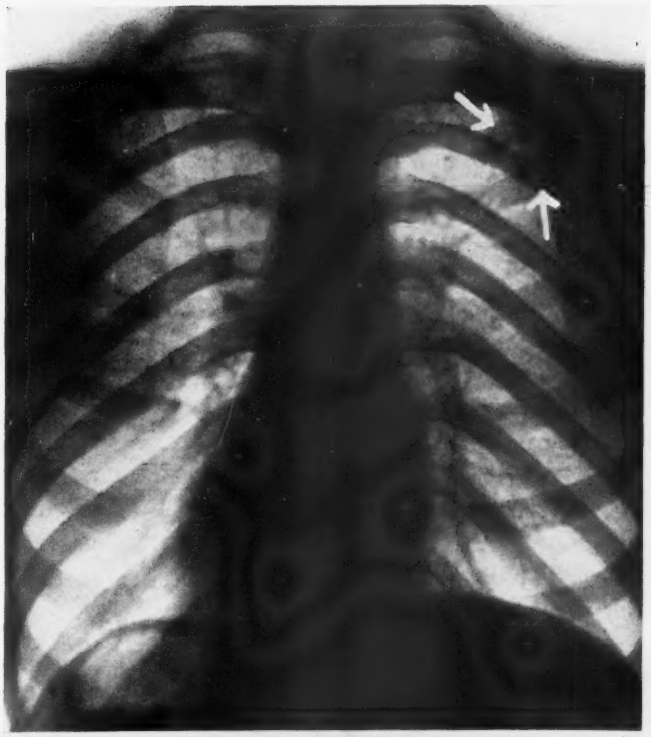
[3] After this paper was in the hands of the printer, my attention was drawn to the fact that these infraclavicular infiltrations were described by an American before Assmann published his observations. In Jaches and Wessler's "Clinical Roentgenology of Diseases of the Chest," published in 1923, Dr. Harry Wessler publishes several excellent roentgen pictures (see especially figures 20–25) clearly illustrating these lesions. In the text it is stated that "the earliest evidences of the disease (pulmonary tuberculosis) are less often found in what is clinically known as the apex than in the infra-clavicular region. Furthermore, the axillary half of the lung is more apt to be involved in the beginning than the mesial half" (p. 69). Wessler also states correctly that the physical signs of these lesions are not clear and "may come to light only later when the process has extended to the apex." Under the circumstances the priority belongs rather to Wessler than to Assmann, who has universally been given this honor by German authors.

toms. This point is well illustrated by the following examples of a relatively common group of cases:

Case 1: D. S., male, aged 28. *Family and past history* is negative, except for influenza, from which he suffered five years ago, and an operation on the nasal septum two years ago. He felt well till the autumn of 1926, when he began to cough and tire easily at his work. In January, 1927, he expectorated some blood, and on careful thermometry a rise in temperature was elicited, some afternoons reaching 100°F. Examination of his sputum revealed *tubercle bacilli.* He lost 10 pounds in weight within two weeks after the haemoptysis. Careful *physical examination* failed to elicit any positive signs of a pulmonary lesion, except for some impairment of resonance on the right side above the second rib which may be found in healthy people. But on the *roentgenograph* (figure 1) there is to be seen a soft homogeneous shadow below the right clavicle at the periphery of the lung field. The rest of the lung appears entirely negative, except for a small calcified nodule in the left fourth interspace near the hilum. The patient was advised to go to a winter resort near the city, where he remained for seven weeks at rest. He returned in excellent condition, having gained 29 pounds in weight. He has been attending to his business for the past eight months without symptoms of relapse.

Case 2: J. C., female, aged 28, laboratory worker. Has been troubled with colds, which she attributed to tonsillitis, for a year. In August, 1926, tonsillectomy was performed without marked relief. Since October, 1926, she has had cough, expectoration, slight fever, 100°F. afternoons, and night-sweats. She has lost 10 pounds in weight in two months. *Tubercle bacilli* were found in her sputum. *Physical exploration* failed to elicit definite signs of a localized lesion in her lungs. The *roentgenograph* showed a soft and partly striated shadow in the left lung on a level with the third interspace and calcified foci scattered throughout both lung fields. Both apices appeared free from pathological changes. During a stay at the Bedford Sanatorium for six months the constitutional symptoms disappeared and she gained 12 pounds in weight. She was discharged as a patient, and has since been employed as technician in the laboratory.

We are evidently dealing here with patients, who have constitutional symptoms of chronic pulmonary tuberculosis but in whom physical exploration of the chest fails to reveal reliable signs of a lesion in the lung. Only the cough, blood-spitting, loss in weight, malaise and, above all, tubercle bacilli in the sputum, lead to a diagnosis. The lesion is localized only by the roentgen rays, and is found, not in the apex, but below the clavicle. From the roentgen-ray picture it is clear that the lesion is



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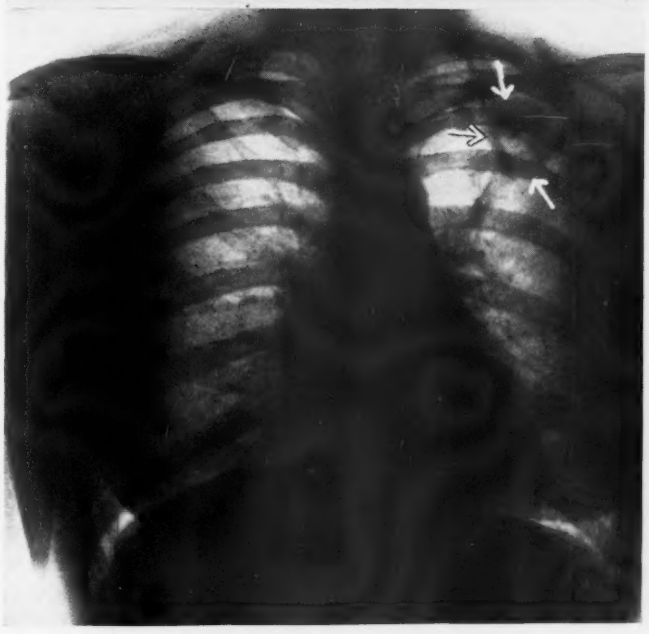

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FIG. 1. *Case 1.* Infraclavicular infiltration in the right lung
FIG. 2. *Case 5.* Isolated infraclavicular cavity in the left lung

of the exudative, bronchopneumonic type of tuberculous infiltration. It is not made up of the stippling, characteristic of submiliary or conglomerate tubercles, seen in acute progressive cases of phthisis, nor of the clover-leaf spots typical of a certain group of early lesions. These infiltrations appear as soft, cloudy, almost homogeneous, isolated patches, the size of a cherry to that of a pigeon's egg, in the midst of apparently healthy lung tissue. In the centre we may at times make out a kernel of deeper density. The margin of the shadow is usually irregular, but now and then it is clear-cut and sharply demarcated. These shadows are in many cases located near the periphery of the pulmonic field, but are met with in exceptional cases in any place of it.

In a large proportion of cases the disease runs a mild, benign course; the infiltration is absorbed within a few months, hardly leaving anything to indicate its previous location, or linear shadows, characteristic of sclerosis, remain on the roentgenograph. In rare instances the lesions becomes calcified, as in the following case:

Case 3: S. D., female, aged 26. At 18 she coughed, expectorated and lost in weight. *Tubercle bacilli* were found in her sputum. She was admitted to a sanatorium, where she remained for nine months. She returned and has felt well since; married, and gave birth to a healthy baby. There are no *physical signs* discernible to indicate the location of a lesion, but on the *roentgenograph* a deep shadow, indicative of calcification of an old lesion, is clearly visible in the left infraclavicular region.

But calcification of such a lesion is rare. More commonly in progressive cases the infiltration undergoes liquefaction and a cavity is formed, as in the following cases:

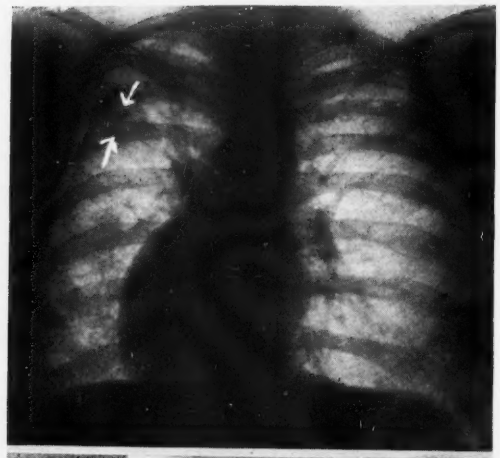
Case 4: H. S., male, aged 23. Coughs since August, 1926, and was treated for bronchitis. Progressive loss of weight, malaise, pain in chest and slight haemoptysis urged him to seek admission to a hospital, where a roentgenograph and *sputum* examination were found *positive* for pulmonary tuberculosis, and he was referred to Bedford Sanatorium. *Physical signs* on admission were those of fibrocaseous lesion in right upper lobe,—impairment of resonance, bronchial breath-sounds and medium-sized moist râles above the third rib anteriorly and over the upper half of the interscapular space posteriorly. *Roentgenograph* showed shadow indicating extensive infiltration of right infraclavicular region, part of which is rather bright, with a circular shadow around it. Lower down, thickened interlobar fissure seen. Except for some slight stippling, apex, visible above clavicle, not involved. However, course of

disease has been rather favorable, despite presence of excavation. Temperature declined to normal soon after rest treatment was instituted, and patient has been gaining in weight and strength.

Case 5: F. G., female, aged 36. Except for an attack of typhoid at 18 she had always felt well till two years ago, when she began to cough, and noticed streaks of blood in her sputum and lost in weight. *Tubercle bacilli* were found in her sputum. She was advised to go to the mountains, where she recuperated within four months. She then returned to the city and to her work, but because of a relapse of the previous symptoms she had to resume rest treatment. *Physical examination* elicited signs of a lesion in the left upper lobe. A roentgen picture (figure 2), taken August 11, 1926, shows a circular shadow, the size of a large plum beneath the left clavicle. The thickness of the wall around the rarefied area precludes its being one of the so called pleural annular shadows which will be discussed later on, but is undoubtedly representing an excavation. The shadow extending from the cavity to the mediastinum is linear, indicating a reparative process. Both apices are apparently free from changes.

Case 6: C. B., female, aged 19. Her sister died from tuberculosis two years ago, and at that time she was examined at the Montefiore Hospital, a roentgenogram was made of her chest, and it was found that she was free from pulmonary disease. She had been troubled with frequent sore throat, and for that reason tonsillectomy was performed when she was 15, and at 16 she was operated on for appendicitis. Since April, 1927, she has had a dry hacking cough, and at times her sputum was tinged with blood; in May, 1927, she had a fairly copious haemorrhage which was repeated one week later. On admission, June 26, 1927, we found slight impairment of resonance over the left upper lobe, but no decisive changes in the breath-sounds, nor any adventitious sounds. A *roentgenograph,* taken April 15, 1927, showed an infraclavicular infiltration at the periphery of the lung field in the second left interspace (figure 3). The rapidity with which cavity-formation is apt to occur in these cases is seen in the picture (figure 4) taken July 3, 1927, which shows a circular shadow in place of the infiltration three months before. It will be seen that the wall of the cavity is surrounded by a denser shadow suggestive of caseation; the entire centre of the cavity is bright and free from pulmonic markings. Neither apex shows any pathological changes. The hilum shadow is accentuated, and some calcified foci are to be noted there. Artificial pneumothorax was induced, and it will be noted (figure 5) that the cavity was not obliterated, which shows clearly that we are not dealing with a so called pleural annular shadow.

[3



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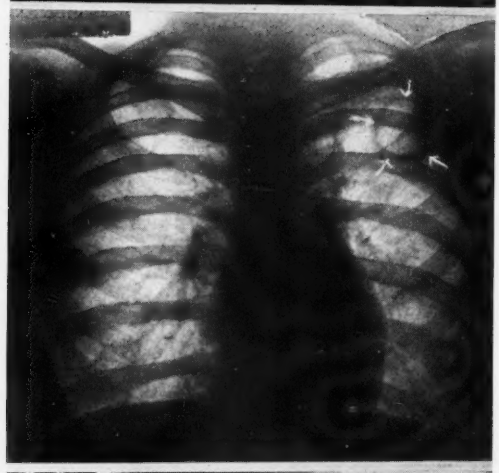

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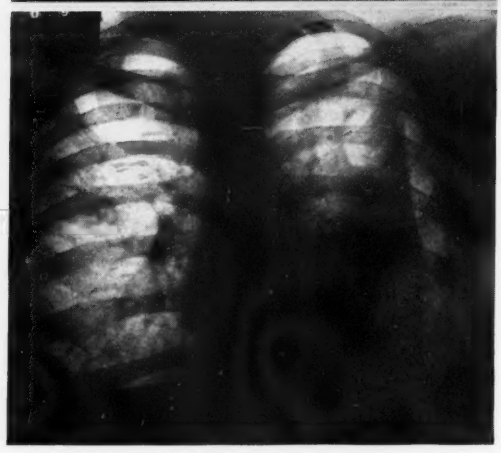


FIG. 3. *Case 6.* Infraclavicular infiltration in the left lung. Roentgenograph made April 15, 1927.

FIG. 4. The same case as in fig. 3. Roentgenograph taken July 3, 1927, showing rapid excavation in place of the infiltration.

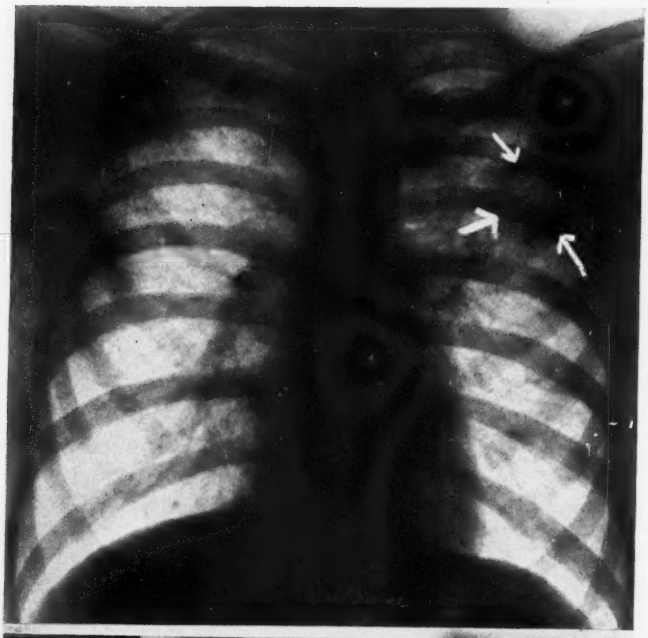
FIG. 5. The same case same as in figs. 3 and 4. Artificial pneumothorax and picture on September 2, 1927. The cavity remained, showing that there it is a parenchymatous cavity, and not a pleural annular shadow.

In most cases these isolated cavities are found just below the clavicle, but now and then we meet with them much lower down in the lung. The following case illustrates early cavitation in the lower lobe:

Case 7: M. A., female, aged 26, a recently arrived immigrant from Eastern Europe. "Never sick" in her native land, even during the World War, when her city was invaded by hostile armies several times. But since she came here three years ago she has been coughing, and losing in weight and strength. She continued at her occupation till blood-spitting induced her to consult a physician, who found *tubercle bacilli* in her sputum. She was sent to the mountains, where she regained her normal weight within a month and felt as

FIG. 6. *Case 7.* Infiltration with excavation in right lower lobe

if she were fit to resume her work. But another attack of haemoptysis urged her to seek admission to Bedford Sanatorium. *Physical examination* of the chest on admission proved entirely negative; no lesion could be localized with certainty. The *roentgenograph* (figure 6) showed a circular shadow, the size of a hen's egg, on a level with the sixth and seventh interspaces in the right side. A *roentgenograph,* taken four months later when her general condition had improved to a noteworthy degree, showed that the cavity had shrunk to about half its original size. In fact, under the routine treatment in the sanatorium she soon became afebrile, gained in weight, and asked to be discharged, feeling that she was fit to resume her occupation.



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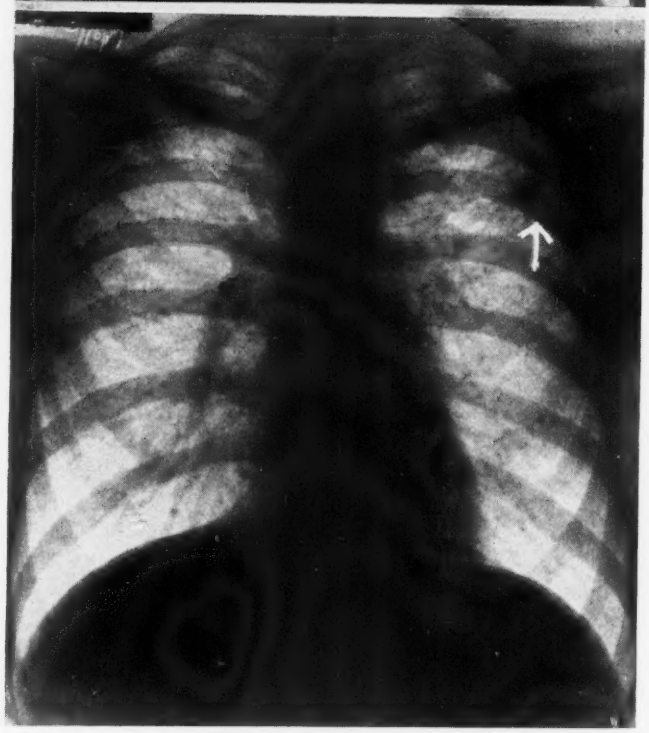

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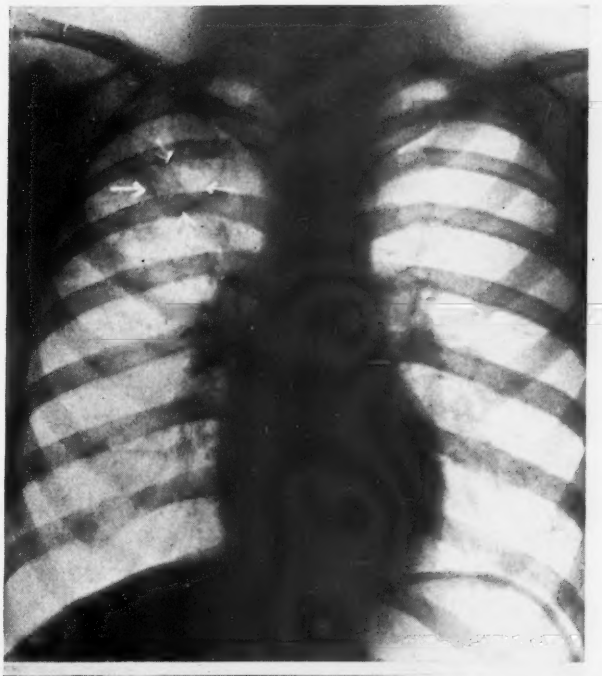
FIG. 7. *Case 8.* Infraclavicular infiltration with excavation in left lung. Roentgenograph taken November 24, 1926.

FIG. 8. The same case as in fig. 7. Picture taken March 18, 1927. The cavity disappeared leaving a dense scar.



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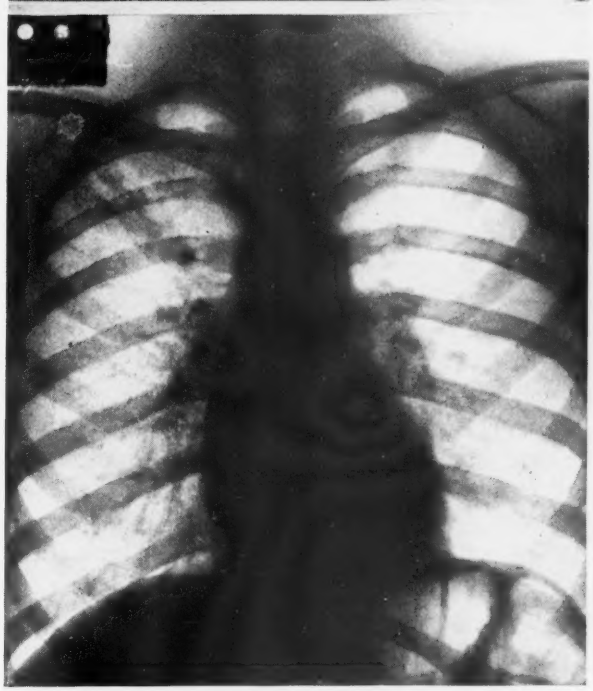

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FIG. 9. *Case 9.* Roentgenograph taken March 22, 1927. Infraclavicular infiltration, with isolated cavity in right lung.

FIG. 10. The same case as in fig. 9. Roentgenograph taken September 23, 1927. The excavation and infiltration disappeared, leaving a linear scar.

The improvement in these cases is at times astonishing; serial roentgenographs may show that the cavity, even when of substantial size, has healed, leaving merely a striated shadow to indicate its conversion into connective tissue. The following are illustrations of such cases:

Case 8: G. B., male, aged 19. Mother had diabetes, and succumbed to complicating pulmonary tuberculosis. Nothing in *personal history* with any bearing on present trouble. Began to cough November, 1925, had fever, and was laid up for several weeks; treated for bronchitis. Recuperated and felt well till June, 1926, when again began to cough, lost in weight, and felt weak; fever 100.6°F. afternoons, and night-sweats. In November, 1926, examination of sputum revealed *tubercle bacilli. Physical exploration* failed to elicit definite signs of localized lung lesion, but *roentgenograph* (figure 7), taken October 24, 1926, showed a circular shadow in the third left interspace toward the periphery of the lung field, while the apices were apparently free from abnormal shadows. Remaining at the sanatorium for a few months he became afebrile, gained 12 pounds in weight, and was found fit for work in the occupational-therapy department of the institution. A new *roentgenograph* (figure 8), taken March 18, 1927, showed no indication of the excavation clearly visible on the picture taken five months before. Instead we may note a shadow indicative of sclerotic tissue.

Case 9: S. M., male, aged 18. Subject to colds and treated for bronchitis for four years. In December, 1926, began to cough, ran fever up to 103°F., had night-sweats, and expectorated small quantities of blood several times. *Tubercle bacilli* found in sputum. Admitted to Bedford Sanatorium March 21, 1927. *Physical exploration* elicited presumptive signs of lesion in right upper lobe. On *roentgenograph* (figure 9), taken March 22, 1927, infraclavicular infiltration with excavation seen, as well as dense shadow at right hilum, indicative of enlarged and probably caseous lymph nodes. Remaining in sanatorium for six months, at first at complete rest, temperature declined, and for past two months has not exceeded 99°F., toxic symptoms disappeared and patient gained 11 pounds in weight. New *roentgenograph* (figure 10), taken September 23, 1927, shows circular shadow entirely disappeared, leaving some striated markings indicative of connective-tissue formation, while caseous lymph nodes at right hilum show marked diminution in size and tendency to sclerosis.

The shrinkage of these cavities and, at times, their complete obliteration, as is seen from the cases just detailed, throw new light on certain aspects of the pathology of tuberculosis and, from the practical aspect, on the prognosis of pulmonary cavities. In this country, however, the

nature of circular shadows in pulmonary roentgenographs may be questioned by those whose experience in roentgenography of the chest has been extensive. Many papers have been written since the first communication on pleural annular shadows by Sampson, Heise and Brown (18). Some writers believe that the shadows represent pathological changes in the pleural membrane and not at all in the pulmonary parenchyma. Barlow and Thompson (19) and others have seen in them small, localized pneumothoraces, or even hydropneumothoraces when a horizontal shifting level is seen in the most dependent part of the circular shadow. Amberson (20), whose exhaustive discussion of these roentgen-ray pictures should be read by all interested, considers them limited pleurisies, at times associated with separation of the pleural membrane; the resulting interstice may contain fluid. However, many authors insist that the shadows all represent pulmonary cavities, and P. K. Brown and Burnham (21) bring some good reasons for this assumption. In the most recent study of these pictures Curschmann (22) advances strong evidence in support of the idea that practically all of them represent pulmonary excavations. However, none of the pictures reproduced here can be considered pleural annular shadows, even by those who believe that some may not be of parenchymatous origin. The capsule of almost all of them is rather thick, the encircled area is markedly rarefied, and the lung markings in the surrounding parenchyma do not extend continuously into the cavity, which would be the case with pleural annular shadows. The mutations of the latter have been emphasized by many writers; they appear and disappear, or change their size and appearance within a few weeks or months, in many cases fading out of the picture altogether. One sign which nearly all writers agree upon is that the induction of an artificial pneumothorax invariably wipes out an annular shadow, while a cavity may remain visible in the picture. In all cases observed by us infraclavicular excavations were not thus obliterated. This was already seen in cases 8 and 9, and the following is another case of this type:

Case 10: G. W., female, aged 16. Had to leave school, November, 1926, because of weakness and malaise after slight exertion. Several weeks later began to cough and had fever. Entered Bedford Sanatorium January 24, 1927. We found the usual signs of a tuberculous infiltration of the right upper lobe. A *roentgenograph* showed an extensive infraclavicular infiltration with cavitation in the right side. Artificial pneumothorax was induced,

attaining but partial collapse of the lung; and it will be seen that the circular shadow below the right clavicle had become even more accentuated than before the pneumothorax was created, which would not have been the case with a pleural annular shadow. The patient has been doing well, the toxic symptoms have disappeared, and she has gained 10 pounds in weight. The sputum contained *tubercle bacilli* on admission, but has become negative. The patient has been employed for two hours daily in the occupational-therapy department of the institution.

Some cases of infraclavicular infiltration are complicated by pleural effusion, as in the following:

Case 11: L. E., male, aged 32. Began to spit blood, September 28, 1923, without any premonitory symptoms. Except for slight hacking cough and expectoration felt as well as ever when blood-spitting ceased within three days. *Tubercle bacilli* found in sputum. *Physical examination* failed to bring forth definite signs of lung lesion, but *roentgenograph* showed patch, located in left infraclavicular region and consisting of soft, cloudy shadow; numerous calcified foci were noted at roots of lungs, but apices were free from pathological changes. Patient advised to go to mountainous region, where he remained for one month and returned in excellent condition, having gained 12 pounds in weight. Resumed activities in his business and continued well till April 14, 1927, when suddenly seized with pain in left chest, fever, dyspnoea, etc. Within few days *physical examination* disclosed signs of effusion into left pleural cavity, confirmed by exploratory puncture. Palliative treatment and rest in bed for a month was followed by absorption of exudate and recovery of weight and strength. *Examination* showed usual sequels of pleurisy,—thickened pleura, slight retraction of chest, etc. On *roentgenograph* the infraclavicular lesion was still represented by sharply demarcated shadow in third interspace. Patient considered fit for resumption of business.

Another form of infraclavicular infiltration is a dense solid mass, running horizontally across the chest and with more or less sharply demarcated limits above and below, simulating an interlobar effusion. In this type of case the constitutional symptoms are apt to be quite severe and the physical signs unmistakable, contrasted with the isolated infiltrations spoken of above.

Case 12: B. S., female, aged 20, admitted January 17, 1927. Began to cough six months prior to admission, lost 15 pounds in weight, and had fever, night-sweats and pain in the left chest. Sputum contained *tubercle bacilli.* After remaining in bed for three months patient became afebrile, but continued to

cough. On admission we found the entire left side of the chest dull on percussion, and feeble bronchovesicular breath-sounds and large moist consonating râles over the upper half. From the physical signs we might have concluded that we were dealing with a caseous infiltration of the entire left lung. But a *roentgenograph* (figure 11) showed a dense shadow, running from the mediastinum across the chest on a level with the third and fourth interspaces, as well as mottling and cloudiness of the lung below this shadow, while the apex was practically free from changes. In the right side there was to be seen an isolated infiltration, with a bright central area below the clavicle. Because the

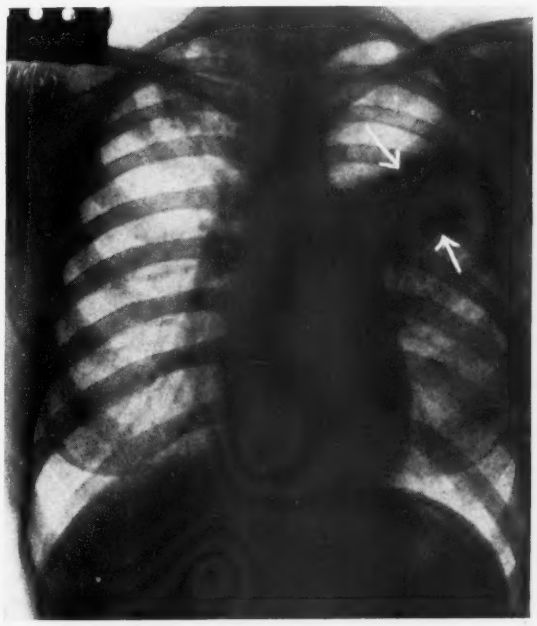

FIG. 11. *Case 12.* Infraclavicular infiltration running across the lung on the left side

constitutional symptoms were in abeyance, palliative treatment was pursued and, at her own request, the patient was discharged greatly improved, with a gain of 8 pounds in weight, on March 19, 1927.

The horizontal shadow in the foregoing case might have been interpreted as an interlobar effusion, but several other cases of this type that came under my observation showed that these infiltrations are apt to soften, leaving a cavity. The following case, in which we satisfied

ourselves that we were dealing with a caseous infiltration, by an artificial pneumothorax and, finally, also by necropsy, illustrates this point:

Case 13: S. L., male, aged 17. Admitted June 26, 1927, with a history of cough, expectoration, fever, emaciation, etc., for six months. The *physical signs* were those of acute pneumonic phthisis involving the entire left lung. The *roentgen-ray picture* showed a dense homogeneous shadow passing across the chest on a level with the fourth to the sixth ribs, sharply delimited above and below with stippling and mottling characteristic of miliary tuberculosis throughout the rest of the right lung except the apex, which was apparently free from changes. The high fever and rapidly progressive course induced us to try artificial pneumothorax as a last resort. It will be noted that the air in the pleural cavity compressed not only spongy lung tissue above and below the infiltration, but also the latter area itself, indicating that we were dealing with an interlobar effusion. The patient succumbed, and at the necropsy the above interpretation was found to be correct.

COMMENT

We have detailed a group of cases of early pulmonary tuberculosis in which the lesion is located below the clavicle, and not in the apex where we expect to find it according to current teachings. In most cases the onset is insidious; the patient has a mild cough, may or may not lose in weight for many weeks or months, has at times a slight subfebrile temperature, and tires easily. Most of these cases are not recognized as early as would be desired, simply either because the patient does not feel sick enough to consult a physician or, even if he does consult one, no decisive physical signs are found. These cases are recognized either by some striking symptoms, such as a pulmonary haemorrhage, or finding tubercle bacilli in the sputum or, what is most decisive, by a roentgen-ray examination of the chest. Even with a good roentgenograph the lesion may be overlooked when it is small, and located toward the periphery of the lung field, inasmuch as roentgenologists expect to find the lesion above the clavicle.

These infraclavicular infiltrations, as is seen from the illustrations accompanying this paper, are represented by soft homogeneous shadows, not unlike those seen in nontuberculous as well as tuberculous pneumonias. Circumscribed patches of this sort are often seen in primary pulmonary lesions in children. And because of this appearance of the infiltrations there arose the problem of whether they represent really

new infections, the very first forming after the initial deposit of tubercle bacilli in the pulmonary tissue.

However, it seems clear that we are not dealing with primary infections. Nearly all cases observed by the writer, as well as those reported in the literature, showed evidence of earlier tuberculous infection, either in the history of the patients, or in the calcified foci discerned on the roentgenographs. The fact that regional lymph nodes are only rarely demonstrably implicated is also strongly against an assumption of primary tuberculous infection. Hence we may safely conclude that these infiltrations have occurred in individuals who, as is to be expected, had sustained infection with tubercle bacilli during childhood.

The important problem is, then, whether these lesions are due to exogenous superinfections with tubercle bacilli brought in with the inspired air, or metastatic superinfections from tubercle bacilli in the intrathoracic lymph nodes carried by the lymph- or blood-stream and lodged at the affected part of the lung. The first cases reported by Assmann (9) were in individuals excessively exposed to sources of tuberculous infection, either because of their occupations or of their intimate contact with patients suffering from advanced pulmonary tuberculosis. This being the case, it would seem that we should have to revise our view of the relative immunity of the tuberculous to exogenous infection with tubercle bacilli, and attempts at prophylaxis would have to take this point very seriously.

But the majority of cases cannot be placed in this category; they apparently have not been exposed to exogenous infection to a greater degree than would be expected of city dwellers. Indeed, I have seen cases of infraclavicular infiltrations in patients with extrathoracic tuberculous lesions for years prior to the onset of the lung disease. It also appears that infraclavicular infiltrations are more common than would be accounted for by excessive exposure. Thus Warnecke (13) found such lesions in 19 out of 739 patients in a sanatorium, that is, in 2.15 per cent of the cases. In our own clinical material the proportion is not less.

I am inclined to believe that the reason why infraclavicular lesions are more often observed in physicians and laboratory workers lies not in greater opportunities for exogenous reinfection, but in the fact that they have greater opportunities and, of course, inclination, to submit to careful roentgenological examination and are more likely than others to have their sputum examined early. Because of the extreme insidiousness of the disease, as was pointed out above, the average person either dis-

regards mild symptoms, such as cough, malaise, loss of weight, etc., or even if he consults a physician the paucity of physical signs precludes costly roentgenological and bacteriological examinations, and the case is treated as a cold, neurasthenia, etc., for a long time, till haemoptysis or some other blatant symptoms make their appearance. This was the case with most of our patients. In two instances haemoptysis, out of a clear sky, was the first symptom and a roentgen-ray examination disclosed the presence of cavities. For this reason only relatively few of these cases are met with in sanatoria, while in clinics, dispensaries and the consulting rooms of physicians specializing in lung diseases they are commonly encountered if looked for.

It is thus clear that we need not discard our ideas of the immunity of the tuberculous to exogenous superinfection with the same virus, and we may consider these infraclavicular infiltrations as set up by endogenous or metastatic reinfections derived from old dormant tuberculous foci, which have flared up for some reason that is unfathomable in the present state of our knowledge of phthisiogenesis. Assmann (9), Romberg (8), Redeker (7), Warneke (13), and others are of the same opinion. I have observed these cases very often in youthful immigrants from Eastern Europe who had gone through the privations of the World War. While in their native lands they held out very nicely, despite starvation and exposure during their formative years; but soon after arriving here, and getting sufficient and nourishing food, they broke down with tuberculosis. Assmann (9) and others have observed the same thing to hold true in Central Europe; during the privations of the war, tuberculosis, though more common than before hostilities began, was of the usual types. But in 1920 and the years since then the juvenile type became more common and infraclavicular infiltrations made their appearance. However, it will be seen that, though most of the cases are met with in individuals between 15 and 25, many are also encountered in older patients. The causes of these phenomena are obscure.

There remains yet to be discussed the tendencies of some of these infiltrations to involution. We have seen that despite the large size and appearance, indicating infiltration of pulmonic tissue by inflammatory exudate, despite the rapid liquefaction and cavity-formation, there may be almost complete *restitutio ad integrum*, or healing by formation of connective tissue, as far as roentgenological appearances indicate. For these reasons, again analogous with tuberculous infiltrations observed in children, some authors have been inclined to consider these infiltrations

as inflammatory and exudative in nature but not entirely tuberculous, etiologically speaking. Eliasberg and Neuland (23) have described such cases in children as *epituberculous* infiltrations, caused, as they allege, by superinfections in tuberculous children with other pathogenic microörganisms, and several authors have described such lesions in adults. Ranke (24) considered such lesions, with proclivities to involution, as due to perifocal inflammations, the result of an allergic reaction of the tissues around the tuberculous lesion which in itself may be comparatively small.

Such allergic reactions are seen at times in tuberculosis patients after injections of excessive doses of tuberculin, when they represent the well-known focal reaction which some authors consider of diagnostic importance. Similar phenomena are noted at times after pulmonary haemorrhages, in which not only the suffused blood affects the appearance of the roentgenograph, but there is also evidence of inflammatory reaction connected with the absorption of the blood and the tuberculous detritus by the pulmonary tissue around the bleeding point, which serial roentgenographs may depict till it is absorbed, and the lung is left intact. There have also been observed more or less evanescent tuberculous lesions, or extensions of lesions in cases treated by excessive exposures to the sun, or such substitutes for sun-rays as the quartz lamp. Moreover, such allergic reactions have been observed in the lungs of tuberculous women during the menstrual period. However, it has not been definitely decided whether these infiltrations are due to allergic reactions of the tuberculous lung tissue, or to superinfection with other pathogenic microörganisms for the ample reason that no autopsies have been available.

SUMMARY

1. Pulmonary tuberculosis with the lesion strictly localized to the apex is, as a rule, benign; though frequent exacerbations of symptoms may occur, the course of the disease is mild, and very few cases develop progressive lesions implicating other parts of the lung, or the larynx and intestines. In other words, apical tuberculous lesions are only rarely fatal.

2. The first localization of the lesion in active and progressive tuberculosis is usually found below the clavicle, toward the periphery of the chest, and at times lower down in the lung. With the advance of the disease metastasis may occur in any other part of the lung; it may spread

upward toward the apex and then we are dealing with a lesion of the upper lobe, but even then its origin has been infraclavicular. These infraclavicular infitrations are mostly seen in adolescents, but may occur in persons over 25 years of age.

3. The first lesion is of the exudative type of inflammation. It may undergo spontaneous retrogression, or it may progress to caseation, softening and cavity-formation. In case the infiltration is absorbed, no trace may be left, or, more commonly, it is organized.

4. At the onset of the disease the subjective symptoms are apt to be mild, or even insignificant for a long time. The physical signs are usually very indefinite, or none can be elicited on exploration of the chest. In many cases cough, haemoptysis, or protracted subfebrile temperature induces a roentgen-ray or sputum examination, which discloses the real cause of the disability of the patient. When physical signs are available, the case has usually progressed to extensive infiltration or excavation.

5. These infraclavicular infiltrations can be localized only on the roentgenograph, in which an exudative patch is found below the clavicle, or an isolated cavity in the midst of apparently healthy lung. Other variaties of infraclavicular lesion are also encountered.

6. Available evidence tends to show that these infiltrations are caused by endogenous or metastatic reinfections from foci dormant since childhood. In other instances they appear to be merely allergic reactions of the lung tissue around slight, hitherto dormant, tuberculous lesions.

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PHYSICAL SIGNS OVER CAVITY IN PULMONARY TUBERCULOSIS[1,2]

KENNON DUNHAM AND ARTHUR P. DERBY

The physical signs over pulmonary cavity are variable, and are often not sufficiently definite to enable the examiner to make the diagnosis. This thought is not new, but its significance is only understood by the clinician of wide experience. It has led us to examine very carefully 71 cases with cavities, to determine, if possible, what simple and easily understood physical signs were to be found over these cavities. While the number of cases is small it is all that we could carefully examine in the time at our disposal. Eight cases had positive physical signs without X-ray evidence. As this is not a study of the comparative value of X-ray and physical signs over cavity we have eliminated these eight cases.

We therefore present only 63 cases with 100 cavities. It is not our contention that the X-ray can detect cavity in 100 per cent of cases, but we are sure that 100 cavities, as shown by the X-ray, existed.

In the Cincinnati Tuberculosis Sanatorium, we check our physical-examination findings by X-ray and our X-ray by autopsy.

In this series of 63 cases, we have had 10 autopsies, and one case was X-rayed after death. All the cavities described were found in the lobes in which they were diagnosed except one. This was described as in the middle lobe and was found in the lower lobe, a mistake in localization, not of diagnosis. Additional cavities were found in eight of these cases, and we have reason to believe that all but one developed between the time of the last X-ray plate and death. This one was an old, small, thick-walled cavity in the left apex, and it probably existed when the last plates were taken before death.

We have grouped the physical signs as dulness, localized coarse râles, pectoriloquy, tubular breathing and amphoric breath-sounds. Positive sputum has been present in all but one case, and because of its great value

[1] From the Cincinnati Tuberculosis Sanatorium and the University of Cincinnati College of Medicine.

[2] Presented before the Clinical Section at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 26, 1927.

we have included it as a most important finding although not a physical sign. We believe that it must always be considered when diagnosing cavity in a case of tuberculosis.

Dulness has been a very general finding. It was found with 93 cavities but was never localized. Like positive sputum it must be carefully considered but it will not localize the cavity.

Coarse râles only suggest a cavity when they are limited to a localized area. The various bubbling metallic and consonating râles are all coarse and have been included under "coarse râles over a localized area."

Pectoriliquy, as we have looked for it, included both the whispered and spoken voice. Thus, under this term we include bronchophony.

Tubular breath-sounds, as understood here, include bronchial breathing as described by others as heard over cavity. The term does not refer to the soft low-pitched sounds heard over the right bronchus of a normal chest at the second interspace, upper right front. Tubular breathing over cavity has a prolonged high-pitched quality on expiration, with a pause between inspiration and expiration. The quality varies from a delicate tubular to a pronounced blowing tone and may even be slightly amphoric. The breath-sounds heard over the trachea best illustrate our idea of tubular breathing.

Bendove (1) makes this statement: "Broncho-vesicular breathing or harsh inspiratory sounds with moist bubbling râles over a limited area in any zone of the pulmonic field below the second rib is very suggestive of cavity." There is probably very little difference between what this author has heard and our findings. We describe his "bronchovesicular breathing" as tubular and his "bubbling râles" as coarse, and we would certainly not rule out of consideration the lung above the second rib.

Cavities in the apices may be easily overlooked by the X-ray, as we have found by autopsy.

Amphoric breath-sounds speak for themselves; but we have included under this head the low-toned cavernous breathing because we were not always certain how other examiners would interpret these sounds and also because they were heard so infrequently.

The cracked-pot sign is bizarre and positive, but it is seldom heard. Auscultatory percussion is purposely omitted. Wintrich's sign was heard but once.

Clinically we have considered the diagnosis of cavity positive when we have had two of these findings present with positive sputum. One case

with persistently negative sputum was diagnosed as positive on the basis of dulness, pectoriloquy and tubular breathing. This diagnosis might be questioned because we did not have positive sputum nor that most valuable sign, localized coarse râles.

Table 1 shows the localized cavities included in this study, with the physical findings and percentage of each.

TABLE 1

Location and features of cavities on physical examination

		DULNESS		COARSE RÂLES		PECTORILOQUY		TUBULAR BREATH-SOUNDS		AMPHORIC BREATH-SOUNDS	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Upper lobes.....	77	77	100	50	64.9	47	61.	35	44.1	9	11.7
Lower lobes.....	23	16	69.5	6	26.	5	21.7	3	13.	1	4.3
	100	93		56		52		38		10	

It is evident that from these figures cavity is more easily diagnosed in the upper (70.1 per cent) than in the lower and middle lobes (30.4 per cent).

Dulness was found over all the upper-lobe cavities (77) but it was only found over 16 lower- and middle-lobe cavities (69.5 per cent).

Coarse localized râles were heard over 50 upper-lobe cavities (64.9 per cent) but over only 6 (26 per cent) of cavities in the lower and middle lobes. This particular finding is somewhat different from our general experience, and we believe that a greater number of cases examined will show a higher percentage of cases with coarse localized râles. Pectoriloquy was heard 47 times (61 per cent) over cavities in the upper lobes and but 5 times (21.7 per cent) over those in the lower and middle lobes. This is in keeping with our general observation.

Tubular breathing was heard 35 times (44.1 per cent) over cavities in the upper lobes and but three times (13 per cent) over those in the lower and middle lobes. This sign is much more pronounced and more frequent when an old fibroid scar has contracted and bound many bronchi together.

Amphoric breathing was heard only 9 times over cavities in the upper lobes and but once over those in the lower and middle lobes. Amphoric breath-sounds, even after we include cavernous breathing, makes a very poor showing, being heard only over ten cavities (10 per cent) and but

once over those in the lower and middle lobes; yet our students are constantly expecting to find these sounds and the cracked-pot sign over cavity.

Dulness has been the most constant physical sign found, yet its value in diagnosis is greatly diminished because it is so frequently found without cavity and because it has not been localized over cavity. We found that, under an area of dulness, localized coarse râles, heard before or after cough, were enough to cause us to suspect cavity. When these findings are associated with positive sputum the diagnosis is almost certain.

Clinically, it is well to remember that pectoriloquy with tubular or amphoric breathing is often heard over old fibroid lesions without cavity. These old scars have little clinical significance unless they contain cavity. If they do enclose cavity, we must expect to hear localized coarse râles and find positive sputum sooner or later.

Thus the finding of localized coarse râles has great clinical significance. A patient with them should receive great care, for at any time he may have a serious spread of infection as well as become a menace to others.

Bendove again says: "One point to be emphasized is that the absence of all classic signs of cavitation does not exclude the presence of a cavity, and no single sign is so important as the total sum of observations and their proper evaluation." We fully agree with both the spirit and the word of this opinion. Not only may we have "silent" and "semisilent" cavities, but it is just as true that we may have very definite signs of cavity when none exists. But this is not so usual.

We have tried to simplify the findings over cavity to dulness, localized coarse râles, pectoriloquy, tubular breathing and amphoric breath-sounds in a manner which third-year students can grasp. We feel that this is necessary because the terms in the literature are confusing, and our medical dictionaries do not clarify them.

We have proved that the findings which are generally looked upon as indicative of cavity are not the most helpful. Pectoriloquy, tubular breathing and amphoric breath-sounds and cracked-pot sounds are most valuable signs; they should always be sought for; but dulness, localized coarse râles and positive sputum afford a quite sufficient basis for the diagnosis of cavity, and are much more common findings.

Since the X-ray is at the disposal of most hospital and chest clinics, we suggest that the time has come to compare carefully our physical and X-ray findings with clinical and autopsy studies, so that the various

chest-signs may be made more simple and their value more understandable to our students. So many physical signs have been overstressed by their finders, and an undue belief in them passed on by students, that a new study of the significance and limitations of physical findings is greatly needed. This report is offered as a slight attempt to meet a part of this need.

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Special Cases

(*Shown by lantern slides*)

Case 1: Sputum always negative. Dulness, localized coarse râles, pectoriloquy and tubular breathing above the second rib and fifth dorsal spine on the left. X-ray shows small cavities in the sixth interspace and between the sixth and fifth ribs on the left. This is an old fibroid case which has been under observation for seven years.

Physical signs were probably due to the trachea, which is markedly drawn to the left, or to contracted lung tissue rather than to cavities lower down under the shoulder.

Case 2: Sputum positive. Dulness, localized coarse râles, pectoriloquy and tubular breathing. It is interesting to note that X-ray shows very small contracted cavity in apex of upper right, surrounded by considerable fibrosis and trachea drawn to right; also scoliosis with curvature to right. Cavity is most frequently diagnosed in such cases.

Case 3: Sputum positive. Cavities seen in upper right gave physical signs of dulness, localized coarse râles, pectoriloquy and tubular breathing. Cavity in left upper between fourth and seventh ribs was not diagnosed on physical examination.

This case was complicated by diabetes mellitus, and such cavities as were seen on the left are often found in these cases, and frequently without physical signs. Typical caseous bronchopneumonia is seen at the right base on the X-ray. (Figure 1.)

Case 4: Sputum positive in February, 1927, and negative in March, 1927. Cavity seen in upper right gave physical signs of dulness, localized coarse râles, pectoriloquy and tubular breathing. A cavity is seen on left, in second interspace close to lateral wall; is without physical signs. Both are shown by X-ray.

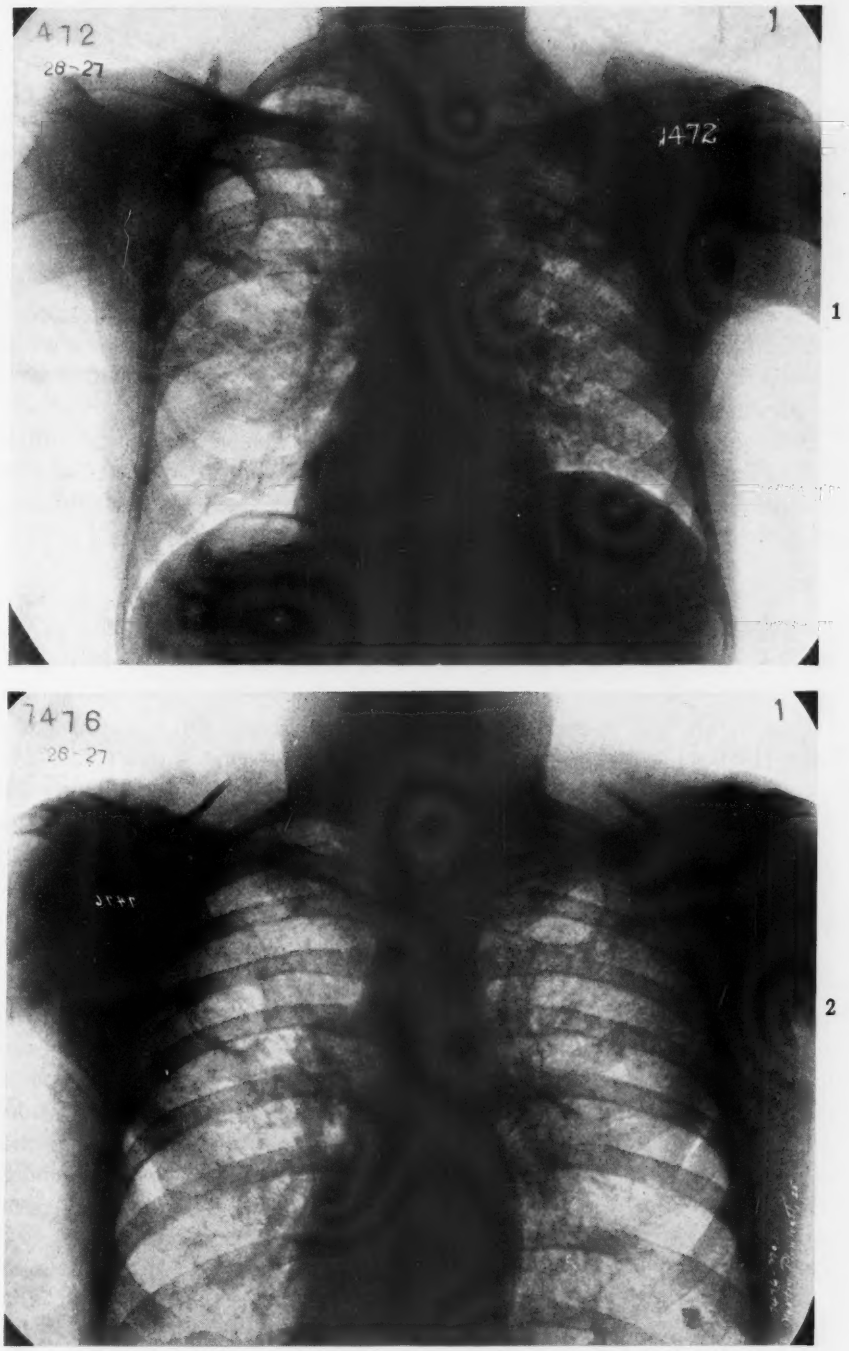


FIG. 1. Case 3. Cavities on right side gave physical signs of dulness, localized coarse râles, pectoriloquy and tubular breathing. Cavity on left side, between fourth and seventh ribs, gave no physical signs. Case complicated by diabetes mellitus.

FIG. 2. Case 12. Thin-walled cavities in both uppers. None of these gave any physical signs of cavity.

Case 5: Sputum positive on admission and negative one month later. Localized coarse râles, pectoriloquy and tubular breathing were found over right upper, posteriorly, as low down as fifth dorsal spine. X-ray shows no signs of cavity. Physical signs were probably due to rather dense fibrosis or contracted cavity which was obscured by fibrosis.

Case 6: Sputum positive. Physical signs in the upper left were dulness, localized coarse râles, pectoriloquy and tubular breathing. X-ray shows small cavities in both apices. Autopsy six weeks later revealed moderate-sized cavities in both upper lobes.

Note the vicious form of caseous bronchopneumonia. The severity of these lesions was proved by the fact that this man died within six weeks. Note the thickened pleura on the right, and the contraction of the ribs and emphysema at the right base.

Case 7: Sputum positive. Dulness and localized coarse râles over the right apex posteriorly. The X-ray shows well-defined cavity, extending as low down as second interspace in front and sixth interspace behind on the right.

Case 8: Sputum positive. Pectoriloquy, roughened inspiration and prolonged high-pitched expiration over the right upper. On the left, posteriorly, opposite sixth dorsal spine, dulness, localized coarse râles, pectoriloquy and tubular breathing. X-ray shows small cavities in the right apex and a larger one below in the second interspace trunks. Left apex also contains cavities. Autopsy, six weeks later, revealed small cavities along the vertebral trunks and much larger cavities below in both uppers.

It is probable the larger cavities developed within six weeks.

Case 9: Sputum positive. Dulness, localized coarse râles, pectoriloquy and tubular breathing over right apex. Probable cavity diagnosed and confirmed by X-ray. Autopsy, seventy days later, revealed a large multilocular cavity, with fairly thick wall, occupying vertebral and first interspace trunks on right. On the left the first interspace trunks communicated with a group of small cavities. There were also a few cavities in the apex of the lower left.

Note on the X-ray the thickened pleura at the right base and emphysema on the left side. No cavities were found by physical examination or X-ray on the left side. These may have developed in seventy days.

Case 10: Sputum positive. Dulness, localized coarse râles, pectoriloquy and tubular breathing were found on the right above the third rib in front and the seventh rib behind. No physical signs of cavity on the left. X-ray shows small cavities in the upper, middle and lower right. Also strongly suggests

cavity in the lower left. Autopsy two months later revealed a multilocular cavity, which replaced the larger portion of the right upper lobe. The lower left was also honeycombed by small cavities. These cavities were all very much larger than shown upon the X-ray two months before death.

Note the vicious type of caseous bronchopneumonia.

Case 11: Sputum positive. Dulness and localized coarse râles between fifth and ninth ribs, posteriorly, on the left, at the time these films were made. X-ray shows cavities in the lower lobe of the left, which seems to contain a fluid line.

Physical examination at the time these next films were taken, eighteen months later, revealed dulness and localized coarse râles, from the fifth to the seventh ribs, posteriorly, on the left. These could not be made out by the X-ray at this time except from study of the previous plates. This shows that a cavity when contracted may not show on the X-ray films.

Case 12: Sputum positive. Thin-walled cavities in both uppers on this film. None of these cavities yield any physical signs; such are frequently described as annular shadows, but they are cavities. (Figure 2.)

Case 13: Sputum positive. In November, 1921, dulness and localized coarse râles were found in the right apex, posteriorly, and a cavity diagnosed. X-ray at that time shows this cavity and also a small cavity in the lower right, posteriorly, in front of the eighth interspace and ninth rib.

On March, 1927, dulness, and localized coarse râles were found above the clavicle on the right and at the eighth interspace posteriorly, on the right, close to the spine. These cavities are definitely shown.

Note that the size and shape of these cavities have changed. The diagnosis of cavity in the lower right was confirmed by physical signs later.

Lateral plates also show cavities.

Case 14: Sputum positive. X-ray shows a large cavity in the upper right which was not found on physical examination. Postmortem lung plates, taken thirty-seven days later, show a large cavity in the upper right and numerous small cavities in the upper left. Autopsy revealed a large thick-walled cavity occupying the upper two-thirds of the upper right; small cavities in the middle right; and a small thick-walled cavity in the extreme apex of the upper left.

It is impossible to say definitely that cavity did or did not exist thirty-seven days prior to autopsy. It is probable that the thick-walled cavity in the upper left did exist and was not found by physical examination or X-ray. Other cavities developed within the thirty-seven days. Note the extreme develop-

ment of caseous bronchopneumonia within the thirty-seven days. This is not uncommon. Notice how closely the postmortem lung plates compare with the necropsy findings.

Case 15: Sputum positive. Dulness, localized coarse râles, pectoriloquy, amphoric breathing and Wintrich's sign on left, above fourth rib and high up in axilla. X-ray shows upper left entirely eaten out by cavities. There is also a small cavity seen in the lower right which gave no signs.

This is our only example of Wintrich's sign. No autopsy obtained. Cavity in the lower right, therefore, is not definitely diagnosed. We are sure it is a cavity and we have so tabulated it.

Films taken after death show that the cavity in left upper is larger and that there is an increase in the caseous bronchopneumonia on the right.

Case 16: Sputum positive. This slide shows definite cavities in both uppers, and an area at the right base in front of the ninth rib suggesting cavitation. None of these cavities were diagnosed by physical examination.

On physical examination, six months later, dulness, localized coarse râles, pectoriloquy and tubular breathing were found over the right upper. The cavity on the left gave no signs. X-ray at that time shows a definite contraction of the cavities in both uppers.

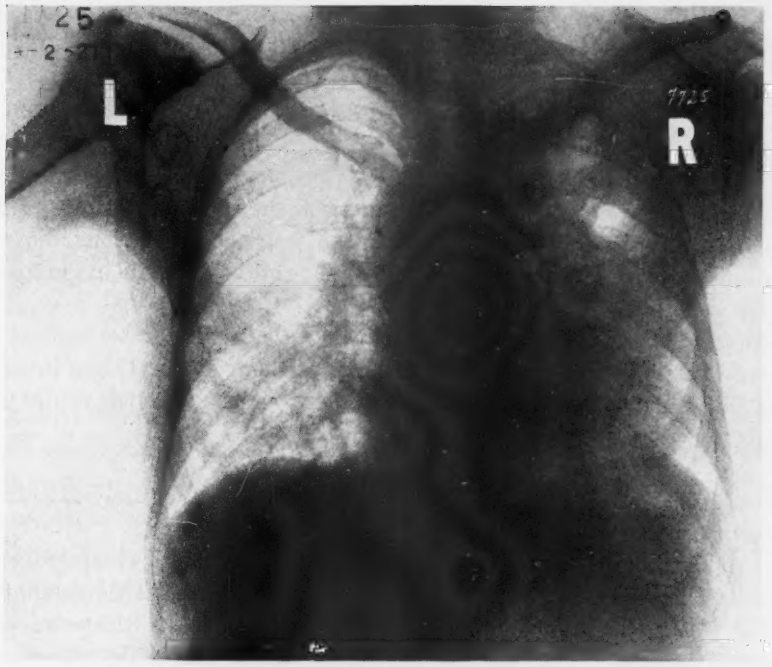
This case demonstrates that signs of cavity are more likely to appear after contraction of these lesions.

Case 17: Sputum positive. Shows a case of transposition of viscera. Heart almost entirely on the right side. Two or more communicating cavities are seen above the heart density, extending to the apex. These cavities could not be made out by physical examination. They were obscured by heart sounds. (Figure 3.)

Autopsy showed large multilocular cavity in right apex.

Case 18: Sputum positive. Physical signs were very definite in the upper right, consisting of dulness, localized coarse râles, pectoriloquy and tubular breathing. In the upper left the physical signs consisted of dulness, prolonged high-pitched expiration and medium râles. This would not justify a diagnosis of cavity. X-ray shows cavity between third and fifth ribs, posteriorly, on the left. (Figure 4.)

Case 19: Positive sputum, March 2, 1927, and negative, April 3, 1927. The cavity in the upper left is clearly shown, and gave no physical signs in November, 1924. The cavity in the upper right, near the upper edge of the third rib along the outer wall, is also without physical signs; and tubercle



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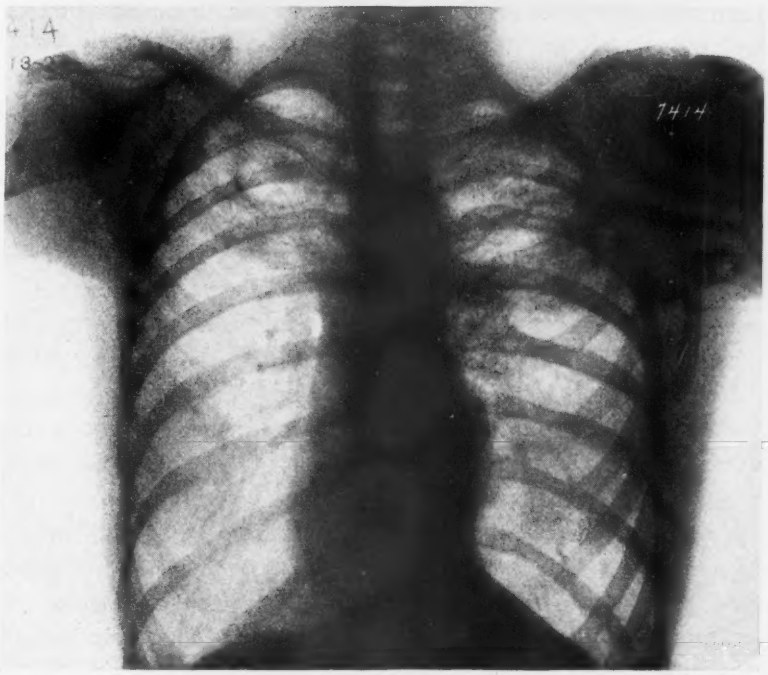

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FIG. 3. Case 17. Transposition of viscera. Two or more communicating cavities above the heart density. Physical signs of cavity, obscured by the heart sounds, were not found.

FIG. 4. Case 18. Definite physical signs of cavity in upper right,—dulness, localized coarse râles, pectoriloquy and tubular breathing. Cavity in upper left, where physical signs were high-pitched expiration and medium râles.

bacilli were found in the sputum at that time. Physical signs of cavity, in 1927, were not found in the upper left or upper right. Signs of cavity were heard opposite the eighth dorsal spine and near the spine on the left. This is shown by the X-ray. These signs are dulness and coarse metallic râles heard over a localized area, and tubercle bacilli were again found in the sputum at that time.

Note: The X-ray suggests cavity in the lower left. But, if we had not had tubercle bacilli in the sputum and had been without physical signs in an old case, which had been taking the cure, the X-ray should not be depended upon absolutely.

Case 20: Positive sputum. X-ray shows the left lung entirely eaten away by cavity, which simulates hydropneumothorax.

The physical signs in this case were dulness, increased whispered voice, prolonged high-pitched expiration and medium to fine râles throughout the right. On the left there were dulness, slightly increased whispered voice, greatly diminished breath-sounds, and an occasional coarse râle. Cavity was not diagnosed clinically on either side. Postmortem lung plates show cavity occupying entire left side, with fluid at base and a large cavity in the upper right. Note the small amount of caseous bronchopneumonia which has developed in about ten months.

THE BRONCHOSCOPIC AND SURGICAL TREATMENTS OF PULMONARY SUPPURATION[1]

EVARTS A. GRAHAM

In the brief time allotted to me for a consideration of this large subject it will obviously be possible only to make certain generalizations and to omit mention of many details which are really important in any adequate discussion of this problem.

The extremely varied features of the pathology of pulmonary suppuration make it impossible to standardize in any way the treatment of these cases, and any plan of treatment in a particular case must be selected with reference to the pathological features present. Thus, for example, of acute pulmonary abscesses there are single large ones and multiple ones. Again, in one case a single large abscess may be located near the hilum and in another case it may be at the periphery of the lung. In other cases there may be an associated empyema, pericarditis, or suppuration elsewhere in the body. An acute suppurative process in the lung may extend, to become a suppurative pneumonitis involving the whole of one lobe or even an entire lung. If an abscess becomes chronic it may be single, with a large or small cavity, or again it may be multilocular. However, in any case there is probably always associated with it some degree of bronchiectasis; and, likewise, in practically every case of bronchiectasis there are also associated abscesses, either small or large. Some chronic cases, however, will present chiefly the features of bronchiectasis, and others the features of abscess. It is very important also in every case of chronic pulmonary suppuration to search for the presence of suppuration in the nasal sinuses, since in many cases the pulmonary suppuration seems undoubtedly to be aggravated by such a condition. Another very important matter, that is seldom considered in the discussions of pulmonary suppurations, is the coincidence of malignant disease of the lung. In the experience of Singer and myself, with 330 cases of pulmonary suppuration exclusive of empyema and

[1] Presented before the Clinical Section at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 24, 1927.

tuberculosis, about 10 per cent have been due to carcinoma of the lung, either primary or metastatic.

The mechanism of healing of an abscess of the lung differs in no essential respect from that of the healing of an abscess in any other organ. The chief peculiarities about abscesses of the lung are their tendencies to become multilocular and the difficulties sometimes experienced in the spontaneous obliteration of the cavities which remain.

Likewise, the principles of treatment of suppurations in the lung are practically the same as those of the treatment of similar conditions elsewhere. These consist of rest, removal of foreign bodies, drainage, obliteration of cavities, and occasionally the removal of chronically infected tissue. The selection of the proper methods for the carrying out of these principles often requires rare judgment based on an extensive experience. The temptation of the ordinary general surgeon is to operate too hastily, too often and unwisely on cases of pulmonary suppuration.

Many cases of lung abscess will heal spontaneously. It is difficult to know exactly how frequently spontaneous healing occurs, because doubtless many of them are cases in which a diagnosis of abscess has not been made. But, from our experience with 330 cases of pulmonary suppuration, Singer and I estimate that about 25 per cent of cases will heal themselves, especially if aided by rest in bed and postural drainage. The most favorable location for spontaneous healing is at the hilum.

The importance of rest in bed, especially during the acute stage, has been particularly emphasized by Pritchard (1) and by Miller and Lambert (2). We also support strongly the importance of absolute rest in these cases. Certainly in almost every case a period of complete rest in bed should be tried before any surgical procedure is undertaken. Foreign bodies should be removed; and often, but not always, prompt recovery follows their removal even though the case is a chronic one. This, to my mind, represents the chief function and value of the bronchoscope.

Drainage, which is naturally carried out by coughing up the pus through the trachea, can be facilitated by various means. A simple and very effective method is by posture, putting the patient in the position which gives the maximum amount of drainage. This can be done best by the use of a specially constructed table. Singer and I feel that this simple method has not received such extensive use as it deserves.

Another method of promoting drainage is by the bronchoscope. It is perhaps unfortunate that I have been asked to discuss the therapeutic uses of this instrument, because my opinion of its value in pulmonary

suppuration is not nearly so favorable as is the opinion of others, except as regards the removal of foreign bodies. The bronchoscopists have yet to demonstrate how efficiently they can treat pulmonary suppuration by their method. It is an astonishing fact that, despite the large numbers of cases that have been treated with the bronchoscope, I have been able to find published reports of only 13 cases. In 1924 Moore (3), of Jackson's bronchoscopic clinic, published the results of 13 cases, of which number 25 per cent are reported as cured, 42 per cent as improved, and 33 per cent as unimproved. This proportion does not differ greatly from that of spontaneous recoveries, especially when properly directed postural drainage has been carried out. It is also noteworthy that the cases which respond most favorably to bronchoscopic treatments are those which respond the best to postural drainage, namely, those in which the abscess is located at the hilum and has already established a communication with a bronchus.

Another method of inducing drainage is by operation. Ordinary surgical drainage is indicated chiefly in those cases in which the abscess is located at the periphery of the lung, in the cases associated with an empyema, and in those occasional cases in which the natural drainage has apparently become blocked and the process is extending with evidences of marked intoxication of the patient. When drainage is undertaken it should be done through a portion of lung that is adherent to the chest-wall, and therefore a two-stage operation is often necessary, the first stage for the creation of adhesions. However, surgical drainage should almost never be undertaken until after the abscess has reached a subacute stage. It is extremely dangerous to traverse a large zone of oedematous lung tissue in order to reach an abscess.

Compression of the lung for the obliteration of cavities can be performed in several ways. The simplest is by artificial pneumothorax. I shall not discuss this procedure, except to say that in our own experience it has proved itself of great value in many subacute and chronic cases; and that in the subacute cases its chief value is in those in which the abscess is located at the hilum. Two other methods of compressing the lung are represented by the simple means of avulsion of the phrenic nerve in the neck, which produces a paralysis and elevation of the diaphragm on the corresponding side, and by the operation of extrapleural thoracoplasty. Both of these operations should be reserved for chronic cases. Avulsion of the phrenic nerve by itself is seldom effective, but it is often very useful when used in conjunction with other measures.

In chronic cases the comparatively simple measures mentioned above, for the promotion of drainage and the obliteration of cavities, will frequently not suffice. The question, therefore, of the advisability of removal of the diseased tissue has frequently come up. The old operation of lobectomy seemed to have a logical basis, but, unfortunately, the mortality associated with the operation, about 50 per cent, has rendered it almost prohibitive. The principal reason for this high operative mortality has been a suppurative mediastinitis, which seems unavoidable in many cases, owing to the necessity of exposing large raw surfaces on the mediastinal pleura during the process of mobilization of the lobe if it is adherent. A safer method of performing lobectomy in suitable cases has been recently carried out by Whittemore (4), who first removes enough ribs to permit the delivery of the lobe outside of the chest. After adhesions have formed around it the lobe is then removed. This is a modification of a procedure recommended by Lockwood (5) in 1922 for certain cases of pulmonary abscess and one which I have used occasionally for the resection of a portion of a lobe. Whittemore's procedure seems logical and well worthy of trial in proper cases, but in many of those cases in which the clinical and pathological picture is chiefly that of a chronic abscess or multiple abscesses it would seem probably to be impossible to accomplish safely.

For about four years (6) we have been performing another sort of operation on some of the most refractory chronic cases. This operation combines in one procedure all of the principles known to be effective in the treatment of chronic pulmonary suppuration, namely, drainage, compression, and the removal of diseased tissue. The operation consists, first, of an extensive exposure of the lung affected. Then, without separating adhesions, but on the contrary establishing them if none already exist, a large area is cauterized with the actual cautery. The idea is to establish numerous bronchial fistulae, through which massive drainage may be accomplished, rather than to remove at first a large mass of lung tissue. It often happens that the effective drainage established in this way, and maintained for a few weeks, is followed by the complete recovery of the patient, so that it is unnecessary to remove a large amount of lung tissue. But, if necessary to remove more tissue at later stages through the same exposure, or after enlarging it somewhat if too rapid healing has occurred, more and more of the lung can be burned out by increasing the depth of the cavity. These cases, after all, present only inflammatory lesions, and the necessity of removing completely all

the diseased tissue is not so great as if they were cases of malignant tumor. Large vessels that bleed during the cauterization are usually clamped and ligated. The wound is packed to avoid further bleeding. Since the blood-pressure in the pulmonary artery is usually only about 20 or 25 mm. of mercury, bleeding from even the large vessels is easily controlled by packing. As a rule the packing is not disturbed for four or five days, and an interval of at least two or three weeks is allowed to elapse between cauterizations. In more than 100 extensive cauterizations, performed in 45 cases, a fatal haemorrhage occurred only once. This was in a child whose haemorrhage happened at night on the twelth postoperative day. If the patient had been an adult, the haemorrhage would almost certainly have been recognized early enough to allow its control by packing. Those who have had trouble with haemorrhage in this procedure have probably made the mistake of not having had a sufficiently large exposure.

The method not only combines in one procedure all the known effective principles in the treatment of chronic pulmonary suppuration, but it also accomplishes each of these principles perhaps more effectively than other procedures. The drainage is copious because of the cross-section of the bronchial tree and the creation of multiple bronchial fistulae. Likewise, compression of the affected portion of lung can probably be carried out more effectively and more precisely by this method than by artificial pneumothorax or thoracoplasty, because the degree of pressure can be regulated simply by the amount of packing in the wound. Finally, as regards extirpation, since the lobe does not need to be mobilized, the mediastinal pleura, pericardium, etc., are not exposed to infection, as is the case when the ordinary lobectomy is done. Therefore, suppurative mediastinitis, the chief factor in the operative mortality of lobectomy, is absent in this procedure. On the contrary, in cautery pneumonectomy an effort is made always to stay inside the lung tissue.

Because of the almost complete absence of shock resulting from the operation it is particularly applicable to many cases which would otherwise seem hopeless. For example, Singer and I have used it successfully in two cases of very severe bilateral suppuration. We have also performed it with a strikingly favorable result in the removal of a portion of a lung that not only contained a chronic abscess but was tuberculous as well, in a man aged 62, who, although completely incapacitated and bedridden for two years before his operation, has now been at work steadily for almost two years, entirely free from symptoms. We have

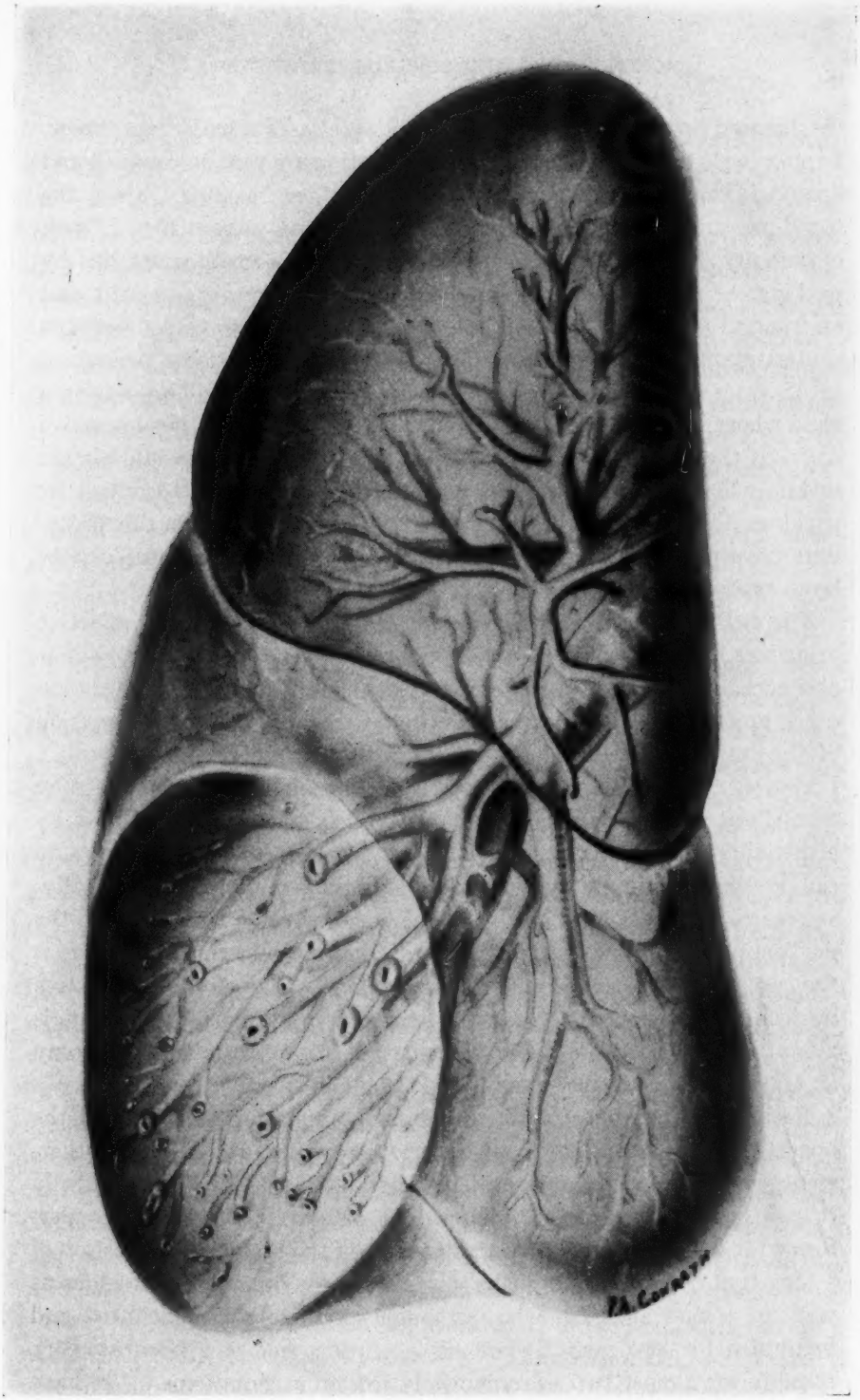

FIG. 1. DIAGRAM ILLUSTRATING PRINCIPLES OF CAUTERY PNEUMONECTOMY, SHOWING THE MASSIVE DRAINAGE ACCOMPLISHED THROUGH NUMEROUS BRONCHIAL FISTULAE

also used it as a palliative procedure in several cases in which a carcinoma of the lung had become infected, with resulting multiple abscesses.

This method has been reserved for only the most refractory chronic cases, but we have applied it in 45 cases. In general, its results have been

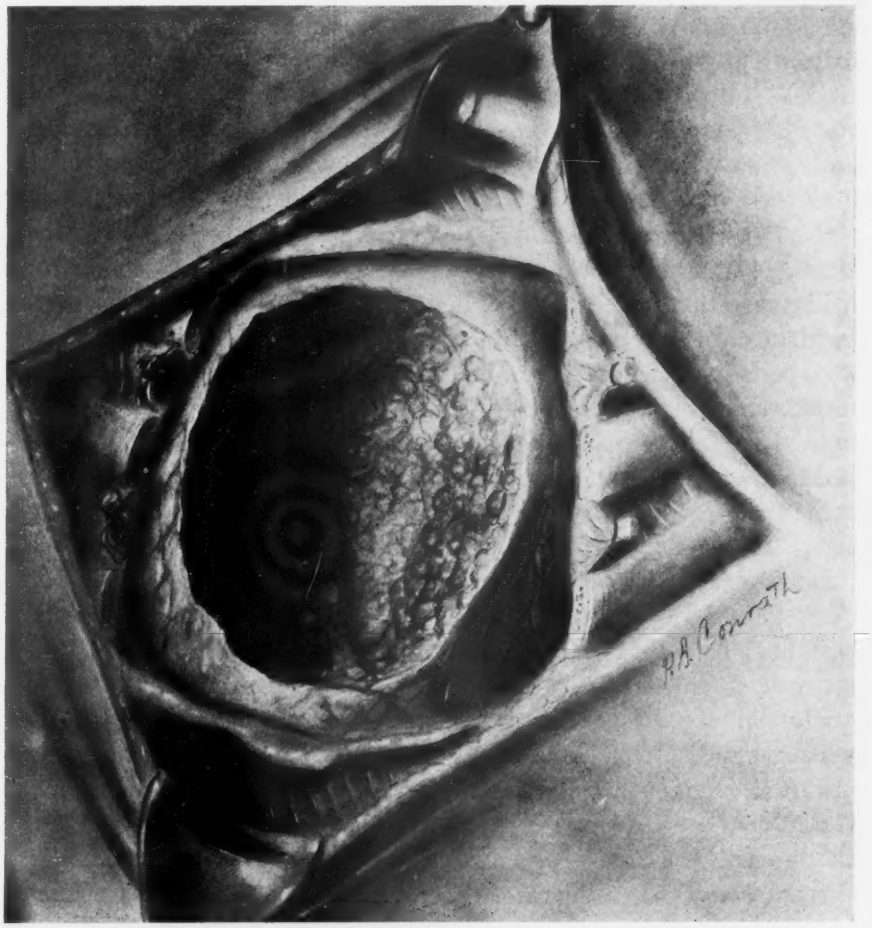

FIG. 2. DRAWING MADE AT OPERATION AFTER COMPLETION OF ONE CAUTERIZATION
It is easy to see how compression can be carried out by packing

better in those cases in which the features of chronic or multiple abscess predominate than in those in which the chief features are those of bronchiectasis; nevertheless, we have had excellent results in both types of cases. The operation has been feared by some surgeons as a dangerous

one, but in our own experience it has not been followed by a mortality which could be regarded as high for this type of surgery. There have been three deaths, which were probably ascribable directly to the operation (a mortality of 6.6 per cent). One of these was in the case of haemorrhage mentioned above, and the other two were due supposedly to air embolism. One other case died of acute cardiac dilatation on the sixteenth postoperative day, and four other cases died later of pyogenic processes elsewhere in the body. One case died from air embolism two years later, after an attempt to close a bronchial fistula; another, at home nearly three years after operation, from an unknown cause, but probably from a recurrent infection of the lung, although the patient had been perfectly well for more than two years; and still another case two years after operation, supposedly from meningitis, indicating also, as in the preceding case, that some remaining infected tissue had caused trouble later. In all, 11, or 24 per cent, of the 45 cases are now dead from all causes during a period of three years since we began using the operation. Several of these cases were known to be desperate risks, but they were operated on in the hope of improving their condition. On the other hand, 31, or 69 per cent, of the 45 cases are free from symptoms. Three patients are still in the hospital, greatly improved. Of the 31 patients free from symptoms, 10 have bronchial fistulae, which, however, do not prevent them from carrying on their ordinary activities. It is possible that other procedures may prove to be more effective in certain kinds of cases; but it seems to me that certain cases, particularly the refractory cases of chronic multiple abscesses, can at present be handled more safely and more effectively by this type of operation than by any other yet suggested. We have used this method also as a palliative procedure in certain cases of carcinoma of the lung associated with suppuration.

Hedblom (7) has reported marked improvement in a series of cases of the bronchiectatic type of chronic suppuration treated by extrapleural thoracoplasty; but in the cases which bore more resemblance to chronic abscess his results were not nearly so good. My principal objection to this type of operation is that the diseased tissue is allowed to remain, from which recurrences may still occur, with the associated danger from haemorrhage, brain abscess, etc. It is not unusual to have symptoms recur a year or two after an apparent recovery if any diseased tissue has been allowed to remain. However, some cases will doubtless be permanently cured by this method; and the operation will probably remain as one of the recognized procedures for suitable cases. Phrenicotomy,

or, better, exairesis of the phrenic nerve, is often a helpful adjunct to any operation, the purpose of which is to secure compression.

In any event, the mortality in any large series of cases of chronic pulmonary suppuration will inevitably be high, because in about 10 per cent of the cases there will be an associated carcinoma of the lung, either primary or metastatic; and in about another 10 per cent cerebral suppuration, either brain abscess or meningitis, will be present.

Various auxiliary measures are important, rest in bed, particularly, neosalvarsan in spirochaetal cases, properly directed heliotherapy, blood transfusions and a liver diet for the anaemia (the latter following the suggestion of Murphy and Minot for pernicious anaemia), and a high caloric diet. It is also possible that lipiodol may have some slightly beneficial therapeutic effect, although it is difficult to understand how it could be of much avail.

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HOSPITALIZATION FOR THE TUBERCULOUS[1]

Its Present Position and Next Steps

JAMES A. BRITTON

This paper attempts to indicate the present facilities in the United States for the hospitalization of the tuberculous; to show in a general way the need for continuing the present plan of hospitalization, the advisability of improving and extending these facilities, the reasons for the supplementing of activities which are directly affiliated with hospitalization, and the urgent need for supplementing all of this by still broader activities in the antituberculosis campaign. No attempt will be made to bring forward any new theories or new ideas.

The published statistics on tuberculosis considerably understate the facts. I do not believe it is necessary to apologize even to Drolet for this statement. The published death-rate from tuberculosis in the United States at the present time is about 90 per 100,000 population. While it is fair to compare this rate with previous reported rates during the last twenty-five years, I question the accuracy of this published rate. Although the records show a little more than 100,000 deaths per year from tuberculosis in the United States, I believe that it is reasonable to suppose that these *reported* deaths do not nearly account for all of those who actually die of tuberculosis. I believe that if a careful check were made on many of the cases reported as pneumonia, empyema, influenza, malaria, typhoid fever, and even malignant diseases, it would be found that quite a percentage of these cases die of tuberculosis. While the apparent average rate, as reported, is reduced in twenty-five years from over 200 to 90 per 100,000, this rate, such as it is, is only a general average.

In certain districts, particularly in the large cities and among certain races, the death-rate from tuberculosis has not been reduced in the last quarter-century. For example, the reported average rate in Chicago for the entire population was 83.2 for the year 1925, which is considerably

[1] Presented before the Sociological Section at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 25, 1927.

lower than the average for the entire United States; but when this rate is separated into deaths among the white race and into deaths among the negro race, it is found that the white race has a rate of 65.7 while the negro race has a rate of 382.5.

There have been many opinions expressed as to the ratio of deaths from tuberculosis to the actual number of open active cases in the community. Wherever the health-department rule regarding the reporting of cases is most effectively enforced, the ratio of open active cases to deaths is about 2 to 1, but often even in these communities it is a well-known fact that many cases of tuberculosis are treated and reported as something else. It is believed that even this ratio is too low and that there are in most congested communities at least three and possibly five open active cases for every reported death from tuberculosis.

The principal reasons why cases of tuberculosis are not reported are two: first, in many cases the diagnosis is not made, and, second, there is still a very decided opposition among some groups of people, and some physicians, to obeying the law regarding the reporting of this particular disease. When the diagnosis is not made, sometimes the doctor on the case is unable to make it, and in other cases the doctor knows the real trouble but, from a misguided sense of responsibility, wishes to save the feelings of the patient and the family.

The point which I wish to make clear is that there is still a large amount of tuberculosis in the community, much more than is ordinarily reported, so that the notion, which has become prevalent in some quarters as to a rapid decline in the amount of tuberculosis in the community, should be accepted with considerable reservation.

If we take for consideration only the deaths which have been regularly reported, then, according to Drolet, the ratio of sanatorium beds to reported deaths in 1924 was, in round figures, 78,000 beds to 102,000 deaths. We are quite sure of the number of beds but the number of deaths was probably understated by at least 25,000; but even if we take the figures at their face value and if we believe in the generally accepted rule of one bed for one death, then the United States is still short at least 25,000 sanatorium beds.

There is much evidence in support of the idea that a case of tuberculosis in any stage has the best chance for arrest or cure in a well-built, well-equipped, sufficiently manned sanatorium. At any rate, there is very little or no evidence to the contrary. There is much evidence to

prove that even six months' training in a well-run sanatorium will give anyone who has had active tuberculosis the knowledge by which he can protect himself and the community from the dangers incident to his infection, as any experienced social worker or field nurse will testify. It is a matter of common knowledge that the health hazard to the community increases with the progress of the disease. In a case of tuberculosis the more ill the patient is, the greater is the need for care and isolation; but isolation without proper care is not compatible with human affection. Science demands isolation for the advanced and terminal cases of tuberculosis, but human sympathy demands adequate care and comfort up to the last breath. There has been no plan devised, to date, which serves this purpose as well as a properly equipped sanatorium.

We speak of the well-built, adequately manned institution. Twenty-five years have seen a tremendous development in our ideas of what should be done for the tuberculous,—developments which have made possible the return to years of health and happiness of many thousands who previously would have been thought hopeless. While of the 78,000 beds now available only too many are still in the old type of flimsy shack or large ward; these at least have pointed the way for a better understanding of the needs and possibilities.

Dr. David R. Lyman recently said:

> Our first idea of a sanatorium was a porch, a reclining chair, a rule book, three quarts of milk and six eggs daily, and a chest examination once a month. In those days a sanatorium was usually conducted by a sick doctor who had been hired principally because of the fact that he was cheap.
>
> We have found out that tuberculosis work, whether in the sanatorium or hospital, requires as high a grade of medical work as that of the most modern general hospital. We know that to get our patients well is the problem of the whole general health and we have not only got to treat the sick lung but everything in that patient that may bring down his general health.
>
> We have got to give thorough general medical service equal to that in any general hospital and we have got to have a medical staff and equipment to give it.
>
> We used to look upon hospitals for advanced cases as having only two functions—removing dangerous cases as foci of infection and giving people a comfortable place in which to die.
>
> The development of pneumothorax and lung surgery has shown us that many of the cases we formerly felt were hopeless have a real chance of getting well. If you provide an advanced hospital with facilities for proper care and equip-

ment you haven't got a home for the dying by any means; you have a hospital in which many people will recover that from our old point of view never had a chance to live at all.

Tuberculosis in the very beginning of the campaign was accepted as a universal community health problem. Hospitalization of one of every three of those with any infectious disease will not solve any disease problem. In tuberculosis at least two-thirds of the infectious-disease problem remains outside the sanatoria. While we may believe and can prove that patients in a well-run sanatorium have a better chance for return to health, it is true that by far the great majority of those who have had tuberculosis never saw a sanatorium of any kind, and it is probably true that this condition will continue for many years, perhaps indefinitely. It then follows that the greater part of all care for the tuberculosis cases will be given outside of institutions, and this in spite of the fact that modern standards for sanatorium care make a constantly increasing demand for such care.

We have no reason to question a program which calls for continued maintenance, and continued development and increase in high-grade sanatoria, but such institutions must be adequately supplemented by a parallel development and multiplication of the facilities for out-patient work. In any given community there is an advantage in the possibilities for close coöperation, if the out-patient or field-service department and the sanatorium are under the same general management. A dispensary system, where periodic physical check-ups are encouraged and where children contacts can be watched and frequently examined, will prevent many potential cases of tuberculosis from developing. A group of well-trained field nurses, actively on duty day by day in the actual places where development of tuberculosis is common, is the first step in the control or spread of this disease.

It is the unusual individual who can afford to have tuberculosis. In many cases social adjustments are necessary even before sanatorium care can be considered, and after sanatorium care has been given there are still more adjustments to be made. Sanatorium advantages, not supplemented by the work of a competent field staff, lose at least one-half in effectiveness as far as the community is concerned.

There is a tendency to emphasize the average conditions or average rates. We say the average tuberculosis death-rate is 90, but we fail to notice, or even speak about, the spots where the rate is 300 or more.

Far be it from me to minimize the great accomplishments made, but there are certain sore spots, particularly in our large cities, which no sanatorium or out-patient department has been able to touch. The tuberculosis rate in these places is as high or higher at the present time than it ever has been. It will take more than the usual antituberculosis program to reduce the disease rate in these groups.

There is no reason to hesitate on an aggressive program for more and better sanatoria. Twice as many patients as are now going could be sent to such institutions and yet not one-half of those who would be greatly benefited by such care and training would be cared for. There is every reason to greatly increase the ordinary field work of every sanatorium unit. These two activities are standardized and recognized for their worth and only need to be strengthened and augmented.

I have absolute confidence in the generally accepted program of hospitalization for the care and treatment of those who have active tuberculosis. I believe that the best and most lasting results are obtained through the sanatorium and its accessory agencies. I most certainly believe all this, but I do not believe that hospitalization of all the open active cases will ever stop the development of these cases in those localities where social and economic conditions are the primary causes.

To plan a system for control of those places where the tuberculosis rate is excessive should be the most important new development in the antituberculosis program,—I say new development advisedly because none of our old plans have worked. To devise a plan which will turn the tide from flow to ebb in the colored settlements of the large cities of this country will require all the wisdom we can muster. Let us not continue to hide behind the favorite explanation of "race susceptibility." After all these years our organization should be strong enough and courageous enough to make all thinking people understand why there are six deaths where there should be but one.

THE ISOLATION OF TUBERCLE BACILLI FROM SEPTIC MATERIAL[1]

H. C. SWEANY AND MAX EVANOFF

In working with the various types of tubercle bacilli we have observed that the successful culturing from lesions depends upon rather small differences in the culture medium and technique of planting. It has been reported by Corper (1) that certain strains isolated from sputum would grow only on media containing egg or serum and that even some of these strains would not bear transplanting. We have observed further that the microörganisms of greatest variability and of lowest vitality are most frequently found in sinuses and enclosed foci. That there are slight differences between different strains of the "human" type of tubercle bacillus is supported by the work of Wulff (2), who found such differences by serological means. He was convinced that human strains were quite different serologically and that the avian type, and perhaps the bovine also, may manifest shades of difference. Karwacki (3) found a range of specific antibodies in pleural fluids that indicated a genesis by antigens of different quality. Although Ross (4) and Griffith (5) dissent from this stand, it seems that the problem is a relative one, and that the differences and variability are what is to be expected from the association of two such biological factors as the tubercle bacillus and its host.

We believe that no one method or medium will successfully apply to all strains of tubercle bacilli. There are certain fundamentals, applying to all, but the finer differences must be detected by a variation of technique in the treatment and cultivation of the suspected material.

In an attempt to increase the percentage results of cultivation, we have rather arbitrarily divided the material into three groups. First, there is that in which there are few non-spore-forming microörganisms. This material may be inoculated on twelve to twenty-four tubes of medium divided into groups of four. By starting with a loopful of pus about nine-tenths is deposited on the first tube and thoroughly spread.

[1] From the Research Laboratory of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

The loop is then applied to tube number two and so on, until four or more have been thus inoculated. There will be a point reached where all contaminating forms will be diluted out and a pure culture of tubercle bacilli obtained. If no contamination exists, obviously the cultures will be obtained more easily.

We have used various modifications of the veal-egg medium of Petroff,[2] but make no claim for their use to the exclusion of others. Several media are to be preferred, for we have found many exclusive growths on some medium or other that ordinarily does not give the best results. Glycerinated potato of various European workers, as well as glycerine-serum or glycerine-blood-agar, are two that we have found to be good to supplement the egg media.

When spores are present the sodium-hydroxide treatment with gentian violet is the method of choice, although the gentian violet should not be used when results can be obtained without it. After a colony appears, its top is scooped off with a small platinum spatula, and these colony crests are treated the same as the material described in the first method.

The third and last group is that in which a large number of non-spore-bearing forms are present. Here chemical treatment must be resorted to. In our hands we have found that sodium hydroxide is the best agent for this purpose. Lurie's results (6) show that this method is better than the antiformin method used by Griffith. It is much better than the original sulphuric-acid method of Loewenstein (7) although his modified methods (8) seem to be quite serviceable.

However, it must not be assumed that the sodium-hydroxide method is without its drawbacks, for it destroys large numbers of poorly walled microörganisms. In one specimen (A175) we found that three per cent sodium hydroxide for twenty minutes destroyed over 80 per cent of the acid-fast granular forms from one lung specimen. In two other instances it apparently "denatured" the germs completely. It is possible that there are at times only a few of the most resistant forms that survive the caustic treatment, leaving the more labile forms to be destroyed. It seems reasonable that any caustic agent, that is intended to destroy contaminations, will destroy tuberculogenic forms in proportion to the resistance of the wall, the length of exposure, and the strength of the

[2] Serum 5 per cent, horse's blood 5 per cent, and potato 20 per cent, added to Petroff's veal-egg medium are three useful modifications. Sterilized milk, in place of water, is also very good. This last mentioned medium, with slight modifications, has enabled us to obtain 95 to 100 per cent results.

TABLE 1

NUMBER	SOURCE AND HISTORY	TYPE OF MICRO-ORGANISM	GUINEA PIG TUBERCULOSIS	HOW TREATED	PETROFF'S MEDIUM		VEAL-EGG MEDIUM	
					Positive	Negative	Positive	Negative
1	Pl. fl. sed. of S. R. 1st	Granules	+	None	0	4	6	0
2	Pl. fl. sed. of S. R. 2nd	Granules	+	None	0	3	1	2
3	Pl. fl. sed. of C. D.	A. F. +	+	None	0	4	4	0
4	Pl. fl. sed. of E. D.	Granules	+	None	0	4	2	2
5	Pl. fl. sed. of G. W.	Granules	+	None	0	4	4	0
6	Pl. fl. sed. of Tikas	Granules	+	None	1	3	2	2
7	Pl. fl. sed. of H. W.	A. F. +	+	None	0	4	4	1
8	Pl. fl. sed of LaV. C.	Granules	−	None	0	3	1*	1
9	Pl. fl. sed. of M. Walsh	Granules	+	None	0	6	1	5
10	Sp. fl. sed. of S. W.	A. F. +	+	None	0	5	0	5†
11	Sp. fl. sed. of Mrs. W.	Granules	+	None	0	4	1	3
12	Sp. fl. sed. of S. S.	Granules	+	None	0	2	1	1
13	Cold abs. 147 (Potts)	Granules	+	None	1	1	1	1
14	Cold abs. (Robt. A).	Granules	+	None	0	6	1	5
15	Cold abs. (John J.)	Granules	+	None	0	4	0	4†
16	Cold abs. (Hugo U.)	Granules	+	None	0	4	3	1
17	Cold abs. (J. H.)	Granules	+	None	1*	3	1	2
18	Local lymph node, guinea pig (U15)	+		None	0	4	1	1
19	Local lymph node, guinea pig (U15)	+		NaOH	0	4	0	0
20	Local lymph node, guinea pig (T99)	+		None	0	10	5(4C)	5(C)
21	Local lymph node, guinea pig (T99)	+		NaOH	0	6	1	5
22	Local lymph node, guinea pig (T58)	+		None	2	2	1	6
23	Local lymph node, guinea pig (T58)	+		NaOH	0	6	1‡	4
24	Local lymph node, guinea pig (T84) 1st	+		NaOH	0	9	3§	6
25	Local lymph node, guinea pig (T84) 2nd	+		NaOH	0	7	3	4
26	Local lymph node, guinea pig (T29)	−		None	0	3	2	2
27	Local lymph node, guinea pig (T89)	+		NaOH	0	9	7	1
28	Local lymph node, guinea pig (B233)	+		NaOH	0	4	1	1
					3.8%		47.7%	

* Egg-milk; milk supplanted water in the preparation of the medium.

† Grew on chocolate-blood-agar only.

‡ Pseudo-tubercle-like microörganism.

§ Non-acid fast tuberculogenic form.

C = Contamination.

Pl. fl. sed. = Pleural fluid sediment.

Sp. = Spinal.

Abs. = Abscess.

reagent. The young microörganisms are sometimes non-acid-fast, and these will be destroyed by treatment. Some older bacilli seem to form heavy-walled granules that resist the treatment better.

A few of our attempts to isolate microörganisms from sources from which they are usually difficult to obtain are listed in table 1. Only egg medium, with and without gentian violet, is listed for the purpose of contrast.

The pleural fluids yielded few negative results on the veal-egg tubes and only one growth on the Petroff gentian-violet medium. In one group (no. 8) a growth was obtained when the guinea pig, killed after six weeks, showed no tuberculosis. This is the second time that we have obtained this result. It shows that our methods are approaching (but not equal to) the accuracy of animal inoculation. The positive results with material from the other sources were still few on the gentian violet and about 50 per cent on the various egg media. The grand average was 47.7 per cent of all tubes on the egg media and 3.8 per cent on the gentian-violet medium. The other media used were little, if any, better than the gentian-violet medium except the chocolate-blood-agar and glycerinated potato. By employing a large number of tubes of these three best media the percentage of positive results was greatly increased.

In two instances (U15 and T99) the detrimental effect of sodium hydroxide on the microörganisms was shown, although there was a greater tendency to produce contaminations without it (T99). The single growth of T58 treated with sodium hydroxide resembled the avian bacillus in growth characteristics and *B. pseudotuberculosis* in staining characteristics and pathogenicity.

The methods were controlled by a series of 96 routine attempts at culturing from sputum, in which 36 good growths were obtained, a slightly higher result than those obtained by Corper and his co-workers (9) but much lower than the original results of Petroff (10).

Finally, two specimens of tissue controls are submitted (table 2). One is from a lung lesion of a patient having lymphogranuloma (A196), in the case of which 8 Petroff tubes and 8 veal-egg tubes yielded luxuriant growths after direct smears from a lesion of practically pure acid-fast bacilli. After sodium-hydroxide treatment 4 veal-egg tubes grew luxuriantly and 4 were negative; on the other hand, 3 Petroff tubes produced one colony each while 5 tubes were negative. A rather unusual fact regarding the three Petroff-medium colonies is that they resembled the avian forms of tubercle bacillus in their growth characteristics and

were apparently the same type as the pseudotubercle bacillus; the microorganism was similar to the one isolated from T58 mentioned above. Both are now being studied for virulence. The other control is from a case of localized caseous pneumonia, autopsy no. 175. Here the first treatment resulted in only three positive growths out of eighteen and these three became contaminated later. The original bacilli were nearly all granular, and most of them were destroyed by the sodium-hydroxide treatment. When these growing cultures were treated, 10 Petroff tubes grew while 8 were negative. Direct inoculations of this culture were impossible. Although practically no coccoid forms were visible by direct smear, an average of 460,000 colonies per gram of the consolidated lung tissue were obtained.

TABLE 2

	PETROFF'S MEDIUM		EGG-VEAL MEDIUM	
	Positive	Negative	Positive	Negative
A196: direct	8	0	8	0
A196: treated with NaOH	3*	5	4	4
A175: treated with NaOH	3	15	—	—
A175: 1st growth treated with NaOH	10	8	—	—
96 consecutive attempts by Petroff's method	36†	60	—	—

* Avian-like in growth characteristics.

† When more than half the tubes showed good growth.

SUMMARY

In the routine cultivation of tubercle bacilli from various pathological sources it is recommended that all material, which contains only a few or no contaminating microörganisms, be directly inoculated on several tubes of each of three or more different media, in such a manner as to dilute out the contaminating microörganisms serially. One of the various veal-egg media has been best in our hands, but it should be supplemented by cooked glycerine-blood-agar and glycerine-potato. These two supplementary media are to be used because no single medium will consistently yield positive results to the exclusion of all others. When non-spore-forming bacteria are present in large numbers Petroff's sodium-hydroxide treatment is recommended. It should only be used, however, when good results cannot be obtained without it, because in one observation we found that as many as 80 per cent of acid-fast forms

were destroyed by it. Furthermore, "denatured" strains were obtained twice following its use. Gentian violet should only be used when so many spores are present that serial dilution following sodium-hydroxide treatment will not dilute them out.

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THE GRANULES OF THE TUBERCLE BACILLUS[1]

H. C. SWEANY

The granules so frequently observed in the tubercle bacillus were known to Koch from the first, but their significance has been the cause of considerable controversy. Mallassez and Vignal (1), in 1883, were the first to express any theory as to their existence. They considered that non-acid-fast granules were forerunners of "zooglear forms" and were capable of growing in a matrix to form zooglear masses of tubercle-forming micro-organisms. Schroen (2), in 1890, observed globular forms of tubercle bacilli, that increased in size and grew to granules that were capable of regenerating tubercle bacilli. Semmer (3), in 1895, saw small globoid bodies, liberated from rods and clubs, reproduce normal bacilli. Crookshank (4), in 1896, mentioned granular forms sprouting into bacillary forms. Schurmayer (5), in 1898, observed non-acid-fast granules multiply as such, or produce rods, and finally develop endospores in coccoid form which developed into bacilli. Arrigo (6), in 1900, described various morphological changes,—from bacilli to granules and back again to bacilli. Ernst (7) in 1902, Meier (8) in 1903, and many others have observed various changes from granules to bacilli. Maher (9), in 1904 and 1910, described a whole cycle similar to Schroen's early accounts. Spengler (10), in 1905, and Much (11), in 1907, carried these observations further, and each claimed a new discovery of a type of granules that received wide attention. Although the granules were observed by numerous workers before, Much seemed to have received the most recognition for his discovery.

It now appears that Spengler's *Splitter*, or fragment, is not identical with any of Much's four forms, yet they are related and are produced by the same general conditions. Bergel's (12) work has done much to clear up their differences; mention will be made of this later. Betegh (13), in 1908, considered the ovoid and globular forms as the initial stages

[1] From the Research Laboratory of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

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of development of the tubercle bacillus. He described a sprouting process, through which thin, straight, non-acid-fast rods are formed from these granules. These rods finally become acid-fast, turn granular, and disintegrate. Knoll (14), in 1910, confirmed and defined Much's work, stating that the granules are essentially endospores and that they work their way through the wall of the bacillus and become free, leaving a vacuole. These granules or "endospores" later sprout and produce acid-fast bacilli. Matson (15), in 1912, was the first to make an extensive search in the sputum of patients having clinical tuberculosis but negative for acid-fast bacilli. In 128 patients, having a definite fibroid tuberculosis but negative sputum by Ziehl's method, he was able to demonstrate "Much" granules, a fact that was confirmed when the inoculated guinea pigs developed tuberculosis. This work, taken as a whole, is one of the best demonstrations of the presence of non-acid-fast granules and their tuberculogenic qualities. Meader (16), in 1915, considered it necessary to examine for Much's forms in suspects before pronouncing patients negative although he believed their presence to be a favorable prognostic sign. By growing culture "801" (the original Koch strain) on synthetic media with various alcohols, Wherry (17), in 1913, produced spore-like bodies in the bacillus and altered the acid-fast staining qualities very markedly. Sorley (18), in 1917, gave a very good review of the subject and confirmed many points, especially the sprouting of granules.

Fortunato (19), in 1922, stated that the granules are found in patients with slight symptoms or latent processes, while the *Splitter*, he thought, occurred in more active processes. Peter (20), in 1922, said that prognosis is much better in cases with Much than with Ziehl types, but that the latter may follow the former in the sputum, because of a difference of resistance in different locations in the lung. In 1922 (and from the time of Spengler), Kirchensteins (21) studied the granules of the tubercle bacillus. This author thought that granules are analogous to nuclear material and that they enter into the process of cell division; and he said that these granules can form new bacilli in the free state but are not to be considered as spores or degeneration forms. Peloso (22), Sivori (23), and Franco (24), in 1924, confirmed the findings of Much, and offered interpretations that differed in detail, but all agreed that they are to be found in the cases of patients with the better prognosis. Fontes (25), in 1926, offered a very scholarly explanation of the formation and disposition of granules in bacteria. He considered them to be nucleate ma-

terial that at first is evenly dispersed but, as it goes on toward reproduction, this material mobilizes into granules, some of which are disposed at the poles while others may be more dispersed. In either case they may enter into the cell division or be extruded, when they are capable of producing new microörganisms. Karwacki (26), in 1924 and 1925, thought that the granules of tubercle bacilli in pleural effusions form mutants of a form with a wide range of characteristics.

In 1926 Sweany (27) reported observations on granular forms of tubercle bacilli, according to which it seemed that the granular forms could carry on an existence as such, and even deteriorate into low-grade or saprophytic microörganisms having a coccoid, bacillary or "diphtheroid" morphology.

It is our purpose to present observations on the various manifestations of cultural, morphological, staining and pathological reactions of the parasite causing progressive tubercle formation in man and animals. While our results do not permit of generalization at present, we nevertheless believe that it is safe to say that the most common acid-fast bacillary form of the tubercle bacillus is not the only manifestation of the etiological agent of tuberculosis, and that the phylogentic aspects of microörganisms, as well as the influence of the animal host and associated microörganisms upon it, have heretofore not been sufficiently understood or emphasized. In the above-mentioned report we were perhaps hasty in referring to the unusual forms as "mutants," because a mutant is a biological term that is itself variously defined. The term "variant" should have been used, and then there could have been no question of its propriety, even though it seems that some of the forms studied consisted of saltatory variations that remained specifically different from the parent form.

EXPERIMENTAL

Our first concrete evidence of the rôle of granules in the life history of the tubercle bacillus was observed in pus from a case of tuberculous otitis media complicating a rapidly progressing pulmonary tuberculosis.

Patient E. B., a young Swedish sea-captain, developed an otitis media that destroyed the tympanic membrane on one side. By means of a long sterile pipette pus was aspirated from the middle ear and examined. An apparently pure culture of tubercle bacilli was revealed on direct smears, practically all of them containing large blue-black granules, either central, bipolar or along

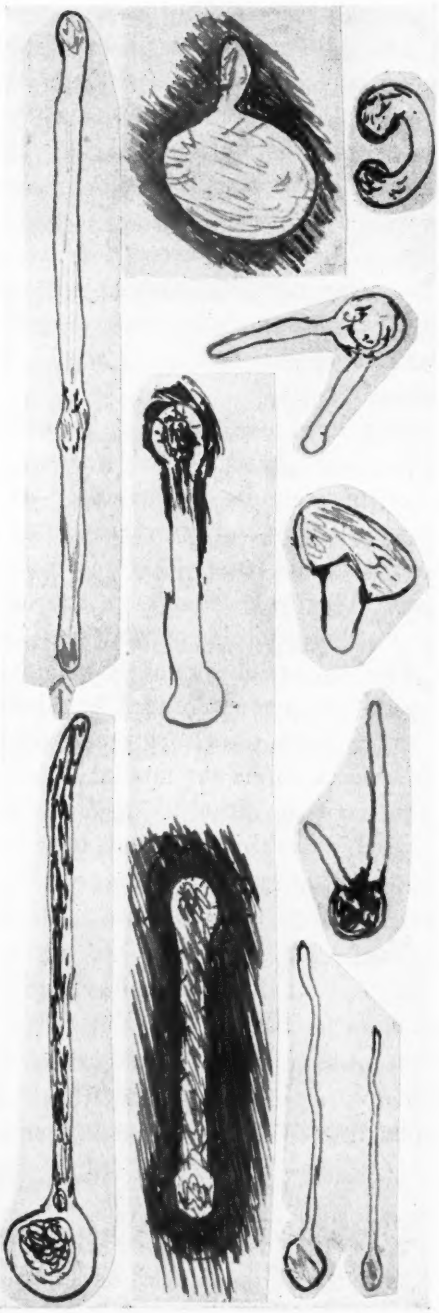

Plate 1

Sketches of dark-field observations on pus from ear of *E. B.*, emulsified in salt solution. Various forms and sizes of sprouting granules are shown.

the body of the bacillus (plate 2, figure 1). Cultures were made on various media, and some of the pus was suspended in sterile salt solution. After three hours and continuously for twelve hours the salt-solution suspension was examined under the dark field[2] and a few of the forms observed are shown in plate 1.

These sketches are taken directly from my note-book, and represent the forms as nearly as I could reproduce them at the time. It seemed that the granules of the bacilli were stimulated to growth by the salt solution. The forms observed were quite variable; most common was a simple sprouting, consisting of a thin motile filament that gradually lengthened during the course of eight hours. Finally the hull was shed off, and a free motile bacillary body was left to move about in the field. Two or three nodes appeared along the body and at both ends of the "bacillus" that appear brighter than the other parts of the body. These bacillary bodies ranged in size from 0.2 micra in diameter to the limit of vision. Sometimes two or more sprouts would come from one granule. Occasionally a large refractile granule would divide into two parts and ultimately into tetrads. The motile bacillary form gradually would become sluggish and come to rest. These bacillary bodies were at first not acid-fast and gram-negative; but it is assumed, for want of direct proof, that they later would take on, at first, slight acid-fastness, and finally all the characteristics of tubercle bacilli. There were no visible forms of micro-organisms from which these sprouting forms could come except tubercle bacilli. Figure 1, plate 2, is a photomicrograph of the direct smear.

Of the various cultures of the pus two glycerine-agar tubes produced unusual growths. All the others were negative for everything but tubercle bacilli. These growths consisted of colonies of tetrads of micro-organisms numbering thousands. Figure 2, plate 2, is a photomicrograph of the microörganism. After transfer to serum-bouillon a culture of "diphtheroid" morphology was obtained (figure 3, plate 2). These microörganisms were not inoculated into animals until after a month on artificial medium. Only a few liver abscesses resulted in the animals after two months. At the time of injection they were not tuberculogenic. The cultural and staining reactions were similar to those of *Staphylococcus tetragenous*. The tubercle bacillus recovered from the patient

[2] Binocular eyepieces give a higher magnification and better visibility when observations are being made on objects smaller than the ordinary bacteria. We use Bausch and Lomb's complete outfit with a pair of 7.5 × oculars.

after death resembled the human type of germ in every respect, and the bacilli in the lung were not granulated, as were those from the ear, suggesting that a separate strain existed in the ear.

A similar type of microörganism was found in the lung of *R. R.*, autopsy 175. Color plate I, figures 3 to 11 inclusive, shows the more resistant forms of this microörganism that are passing through the life cycle of the tubercle bacillus in a salt-solution suspension ten hours old. Simultaneously with this sprouting of the more viable granules is seen a degradation of a certain type of granule that will be mentioned later. The simplest form of granule-sprouting is an unfolding, to form a comma-shaped microörganism with a dark red nucleus and brighter red, curved

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Plate 2

FIG. 1. Direct smear from pus of ear of *E. B.*, showing essentially a pure culture of granular tubercle bacilli. × 1500.

FIG. 2. Type of microörganism that grew on two glycerine-agar tubes in numerous small colonies. × 1500.

FIG. 3. Same as figure 2, grown in serum-bouillon

FIG. 4. Phagocyte in spleen of guinea pig E149, showing numerous granular tubercle bacilli. × 1900.

FIG. 5. Same as figure 4

FIG. 6. Stained smear of an 18-hour-old saline emulsion of spleen of guinea pig E149, showing bacillary pairs, that were seen to come from the large double granules on dark-field observation. × 1900.

FIG. 7. A pair of granules from same source as figure 6, apparently sprouting in opposite direction. × 1900.

FIG. 8. The same emulsion after 36 hours, showing the appearance of cocci, diplococci and tetrads

FIG. 9. After 48 hours. Non-acid-fast bacilli are also represented.

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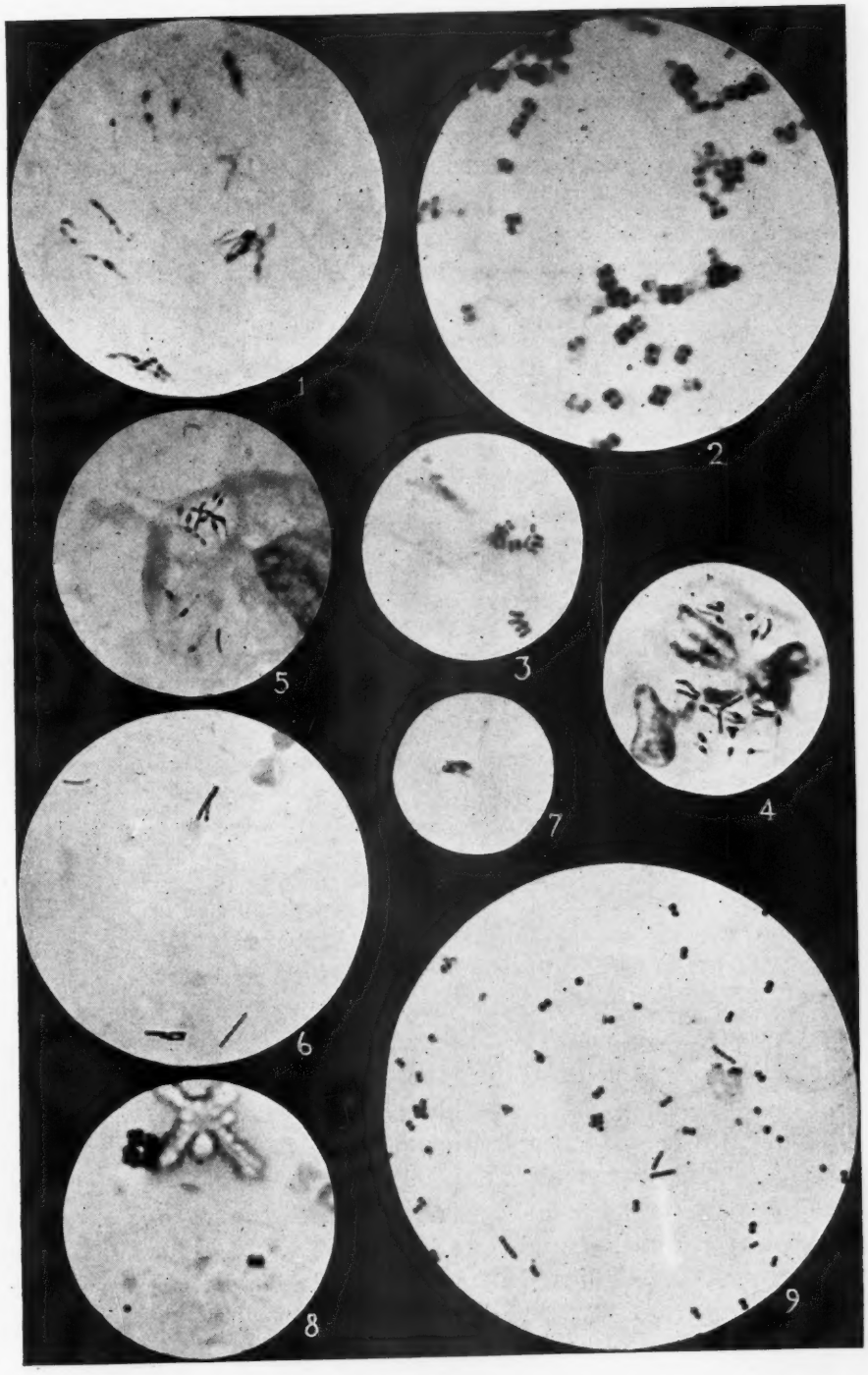
body. In the original granules the substance seems to be rolled up around the edge; and, on germination, it breaks at one point and unfolds as a bacillus. Sometimes the concentrated wax and protein that stains blue-black is left in one end as in figures 3 and 10, or in both ends, as at the upper part of figure 3, or along the body as in figure 4 and the middle of figure 8. Figure 5 appears to represent a bacillus after it is straightened out and the body takes on the bright red color of a young bacillus. This, and those in figure 9 show the characteristic nodes of newly sprouting bacilli. Sprouting may occur by a direct protusion from the wall of the granule as in figures 6, 7, and 13, or may take the form of double sprouts, as in the middle part of figure 8.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In figure 9 are granules that are passing over into bacilli by the simple process of stretching out and ultimately dividing by fission. In the lower left part of the figure is a blue-black granule still in the resting stage. As they emerge into activity progressively the granules take on a brighter red color. They may go on for several generations as acid-fast rods, with an even distribution of the fatty chromatin material, or they may reform more granules and go through the cycle again. The various "nuclei" present may sometimes be seen folded in the original granule by observing them with the microscope slightly out of focus. Many possibilities exist for the mode of germination and the type of micro-organism formed.

Culture 212 was a "sterile" pleural fluid, free from acid-fast bacilli, planted on a special hog-spleen-agar, in which 5 per cent hog spleen was added to glycerine-agar. A five-day growth of this pleural-fluid sediment

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Color Plate I

FIGS. 1 and 2. Drawings of a 5-day hog-spleen-agar growth of culture no. 212, from which a pleural exudate shows only Much's granules. Note the blue granules apparently growing, and occasionally one reverts to the acid-fast form and remains attached to its non-acid-fast mate.

FIGS. 3 to 11 and 13. Showing various modes of sprouting and growth of the granules to acid-fast forms.

FIG. 12. A common weakly acid-fast form seen to emanate from granules (approximately 5,000 diameters).

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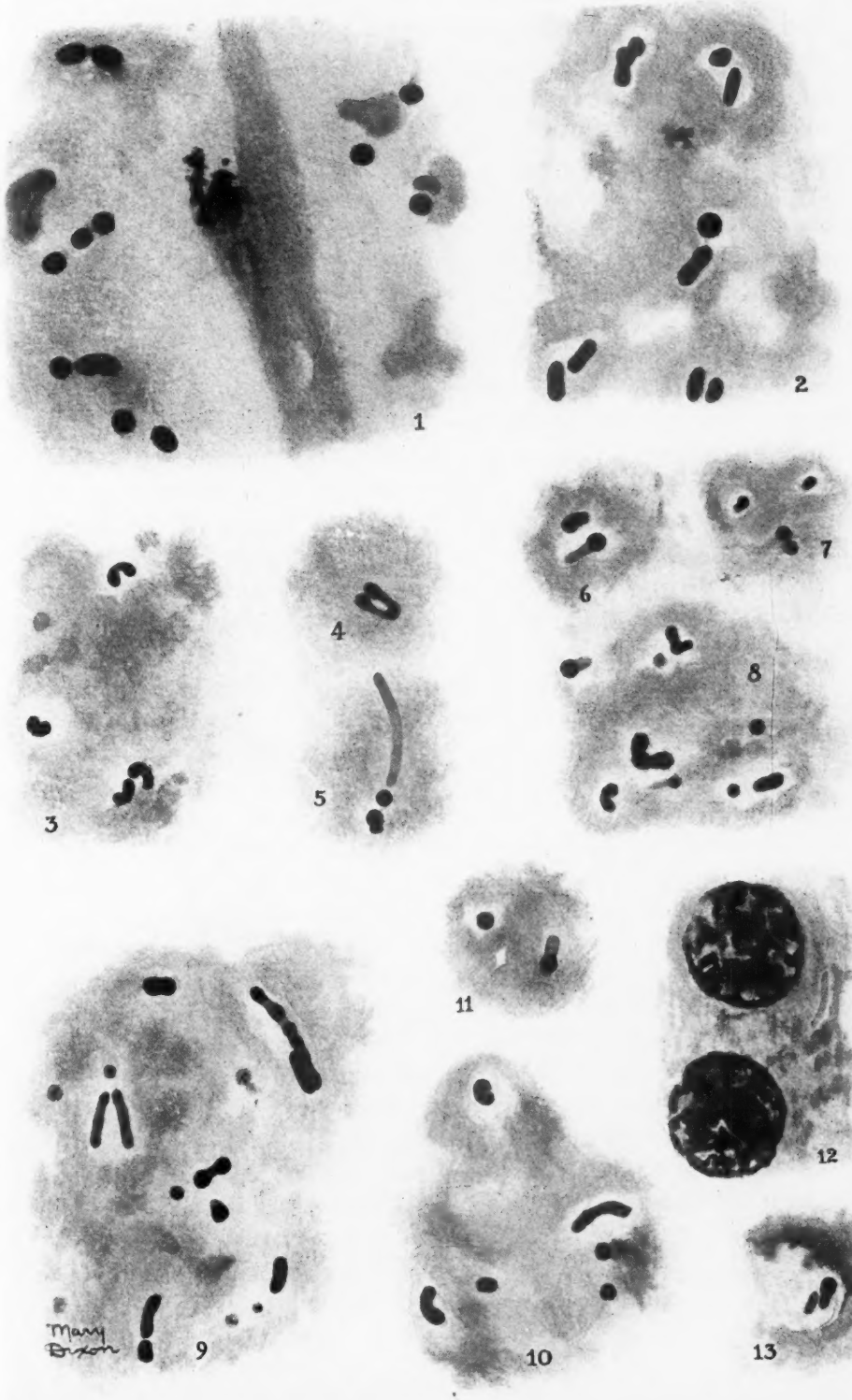
is shown in color plate I, figures 1 and 2. The so called Much granules are much in evidence, as is also the return of some to acid-fastness. Still more interesting are the blue-black forms, apparently growing but not acid-fast. One acid-fast-coccus or bacillus may be observed, joined to its mate, and still having a blue-black color. The acid-fastness of the granules seems gradually to disappear in unfavorable surroundings and ultimately be unable to return. It is a progressive deterioration. As with the preceding illustrations, there seems to be a state reached where permanent non-acid-fast forms appear.

Another study of granules was made on guinea pig E149, which was inoculated from a mannite-bouillon growth of culture 20,676, a pure human type of microörganism as determined by complete animal tests. The various organs of this animal contained different forms of germs. In the lymph nodes and lungs the tubercle bacilli were nodal forms,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with few or no granules. This seems to be a sign of better conditions of growth. There would not appear to be the necessity for the nuclear material to concentrate for self-preservation. In the liver there were small granules in the bacilli and numerous free dust-like granules. In the spleen were very large granular bacilli, mostly contained in monocytes, as shown in figures 4 and 5, plate 2. After placing some of the macerated spleen in salt solution and studying it for several hours it was observed that the heavy double granules would lose their bacillary ends and sprout out in pairs. At first there was a sluggish motility, but after three to five hours the motility ceased. The speed with which these sprouters grew varied widely. Figure 6 represents two pairs of tubercle bacilli from double granules. Figure 7 shows a pair that is sprouting in reverse direction. Of course, these may be in a state of evolution from small bacilli, but they represent the same forms that have been seen to sprout under the dark field. There seems to be some catalytic action required to start the process,—in this case an electrolyte in the presence of free oxygen, without which these changes appear not to happen. If taken *in statu nascenti*, however, and if at the same instant the environment varies sufficiently, a wide range of variations appears to result.

An observation on the pus from a cold abscess, from Dr. E. J. Berkheiser's service at the Children's Memorial Hospital, appears to represent more of a gonidiform type of reproduction of granules. Whether they are tuberculogenic granules or not is uncertain because a peculiar virus, causing progressive emaciation in guinea pigs, existed with the tubercle microörganisms. After two hours in salt solution there appeared matrices, from which protruded very fine motile sprouting bodies having a motility similar to that noted in my first observation. Each of these motile bodies resembled a *caput medusae*. The motile parts eventually freed themselves, and moved around in the salt solution. They were not acid-fast, and they did not give mitochondria reactions. The phenomenon will be described more in detail in a subsequent work with filterable forms. Granules have been observed in a mucoid to waxy matrix and it is possible that such a condition existed here with simultaneous sprouting and transformation to a more rapidly growing variant.

The last observation in this class is one quite similar, and when the origin and fate of the granules were more certain. In this instance a small splenic tubercle from guinea pig T35 was studied. This animal had been inoculated with an unusual form of a human-type germ from patient *S.W.* (autopsy 182), heated to 56°C. for 30 minutes and causing

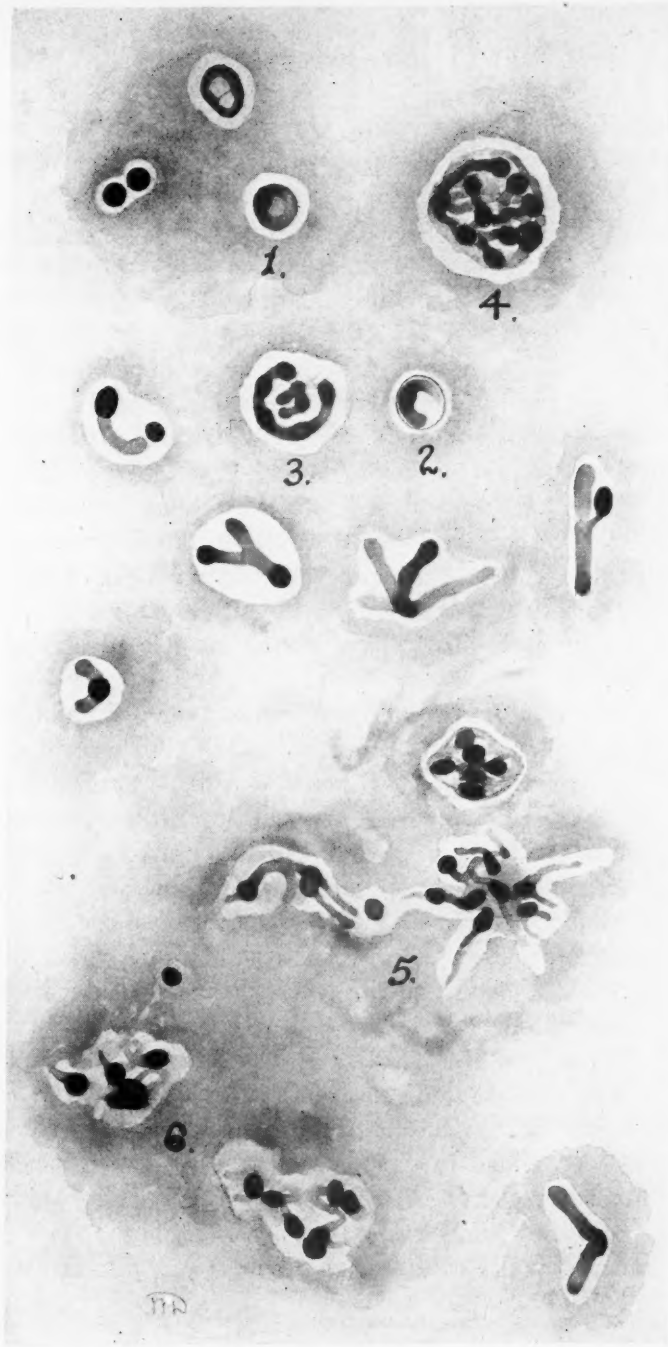

Plate 3

Showing various formations observed in a slide culture from spleen tubercle of guinea pig T35. Figures 1 to 6 seem to show a progressive development from a single granule to a gonidia-like arrangement, from which motile forms appeared to sprout and ultimately return to the granule stage.

a low-grade type of tuberculosis. Nevertheless, numerous refractile granules, that corresponded to one of the Much types, were found in the spleen. Slide cultures[3] were made and studied for twelve days, during which several cycles of change were observed. Plate 3 shows some of these changes. Small nests of granules could be found that would send out motile sprouts. These sprouts would eventually come to rest, when new granules appeared in their bodies. Free granules would enlarge and form comma-shaped or beaded pessary forms. Other peculiar shapes, that are not sufficiently understood to describe, were noted. Similar, but not identical, observations were made on the spleen of guinea pig T34. In this animal only a very few forms, that took a bright acid-fast stain, were present. Many blue-black bacilli and granules, that perhaps corresponded to the bacillary forms described by Much, were also present. Guinea pig T99 was inoculated from T35, and the organs were cultured for tubercle bacilli on egg medium. The microörganism recovered was no different from an ordinary human-strain tubercle bacillus in growth and reaction.

We shall now consider degeneration forms of the granules of tubercle bacilli. In a previous report (27) we brought out evidence to show that tubercle bacilli appear to pass over into non-acid-fast forms under certain conditions. We had pointed out previously that there were several strange phenomena that we could not account for on any basis other than an actual transition of the granules of some degenerate tubercle bacilli into non-acid-fast saprophytes, or perhaps parasites if the "denaturing" stage had not progressed too far. Patient *S.W.* (A175) had, in the apex of the right lung, a localized cone of caseous pneumonia about 10 cm. across, and throughout the tissue there was almost a pure culture of large granular acid-fast bacilli. An average smear contained dozens of bacilli per field, with only a coccus every three or four fields. No other microörganisms were visible. An actual count of ten fields revealed 3 groups of cocci (single or diplococci) and 596 acid-fast bacilli, 483 of which contained one or more large blue-black granules. This made 80 per cent acid-fast bacilli containing the heavy granules. This specimen afforded an opportunity to determine definitely whether certain degener-

[3] The slide cultures were prepared by teasing out the smallest splenic tubercles on a glass slide, macerating them in a drop of sterile salt solution in a sterile test-tube, and adding this to a drop of warm glycerine-agar on a sterile cover-slip. After mixing well a ring of sterile vaseline is made around the agar, and the cover-slip is inverted over a deep culture slide containing a drop of sterile water. The slide is incubated and studied from time to time.

ate forms of granules of tubercle bacilli could become saprophytic cocci.

Several sets of salt-solution emulsions were made up and incubated for study as in the previously mentioned cases.

Contrary to expectations the dark-field examinations did not disclose the sprouting forms observed before. The changes occurred regularly, and were so constant that there seemed to be a definite transition of the larger granules into diplococci and then into tetrads. In three to four hours the large spindle-shaped bacilli, with single refractile granules, were observed gradually to lose their ends; the granule would become larger and less refractile in two to four more hours, and finally a line of cleavage would appear, sometimes longitudinally, but most frequently transversely. After another thirty minutes cross-lines appeared, and tetrads were beginning to take shape. After two hours more complete tetrads were present.

We are not contending that all the tetrads come from this source or that all the granular bacilli underwent this change. It would be impossible to substantiate such a claim, and it would not likely be the truth. However, nothing is more certain than that some of the spindle forms, having a large reddish refractile granule, gradually lost their bacillary ends, became less refractile, and finally changed into tetrads.

These granules appear to undergo a process of ageing, during which some of the larger ones reach a stage of degeneracy in the presence of the requisite stimulation to cease their acid-fast existence. Interesting observations were made on plate cultures, but, obviously, no interpretation can be made when cocci are present, even if the number of colonies present seemed to be too great to be accounted for on the basis of their presence. A thought came to us in this work that there must be some unusual catalytic action that seemed to speed up the germination of these granules, because it was observed that the size and number of colonies increased around the borders of a colony of *Aspergillus fumigatus* that chanced to be present. Some diffusible substance penetrated the medium for 1 to 2 cm., and stimulated the growth reactions.

Plate cultures were made when this and other microörganisms were used to test the theory. *Aspergillus fumigatus* and *Aspergillus niger*, as well as *Staphylococcus albus*, seemed to act as growth catalysts, as shown by the number and size of the colonies. The number and size increased in the neighborhood of the foreign colony.

Because of objections to the emulsion method of study, small cubes,

of 3 or 4-mm. dimension, were incubated in 10 tubes of sterile salt solution, and one was removed every thirty minutes for two hours, then one at 3 hours, 5 hours, 10 hours, and 24 hours. Numerous smears were made, and studied after acid-fast staining. Figures 1, 2, 3, 4 and 5 of color plate II represent some of the degeneration forms observed.

All stages of change could be found at from five to twenty-four hours. The microörganisms protected by phagocytes seemed to remain intact longest. The ones that were free would lose their acid-fast ends as in figure 2 and the larger ones in figure 3. Then all stages of transition over to cocci could be found, with the dark red gradually fading out to a blue, and at the same time there seemed to be a slight enlargement. Figure 4 represents a group having one reddish form dividing, and several blue forms, in various stages of division, showing remnants of the old

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Color Plate II

FIG. 1. Showing a group of granular bacilli from lung of A175 in the early state of degeneration in a 24-hour saline suspension.

FIG. 2. The same type, losing the acid-fast bacillary bodies.

FIG. 3. Granules having lost the acid-fast bacillary bodies, and other granules and coccoids.

FIG. 4. Transitional granules, some of which are definite blue coccoids in bacillary bodies. and one still retains some acid-fastness. See plate 4, figures 3 and 4.

FIG. 5. Showing border-line forms, some reverting to young acid-fast bacilli, as shown by the bright red color.

FIG. 6. Semi-acid-fast diphtheroid forms appearing in a piece of spleen of guinea pig S93, incubated for 3 days in a moist chamber.

FIGS. 7 to 10. Progressive-degeneration form in spleen of guinea pig T35 incubated in the same manner as S93. Figure 10 shows one non-acid-fast diphtheroid form; combination gram and acid-fast stain. (Approximately 5,000 diameters.)

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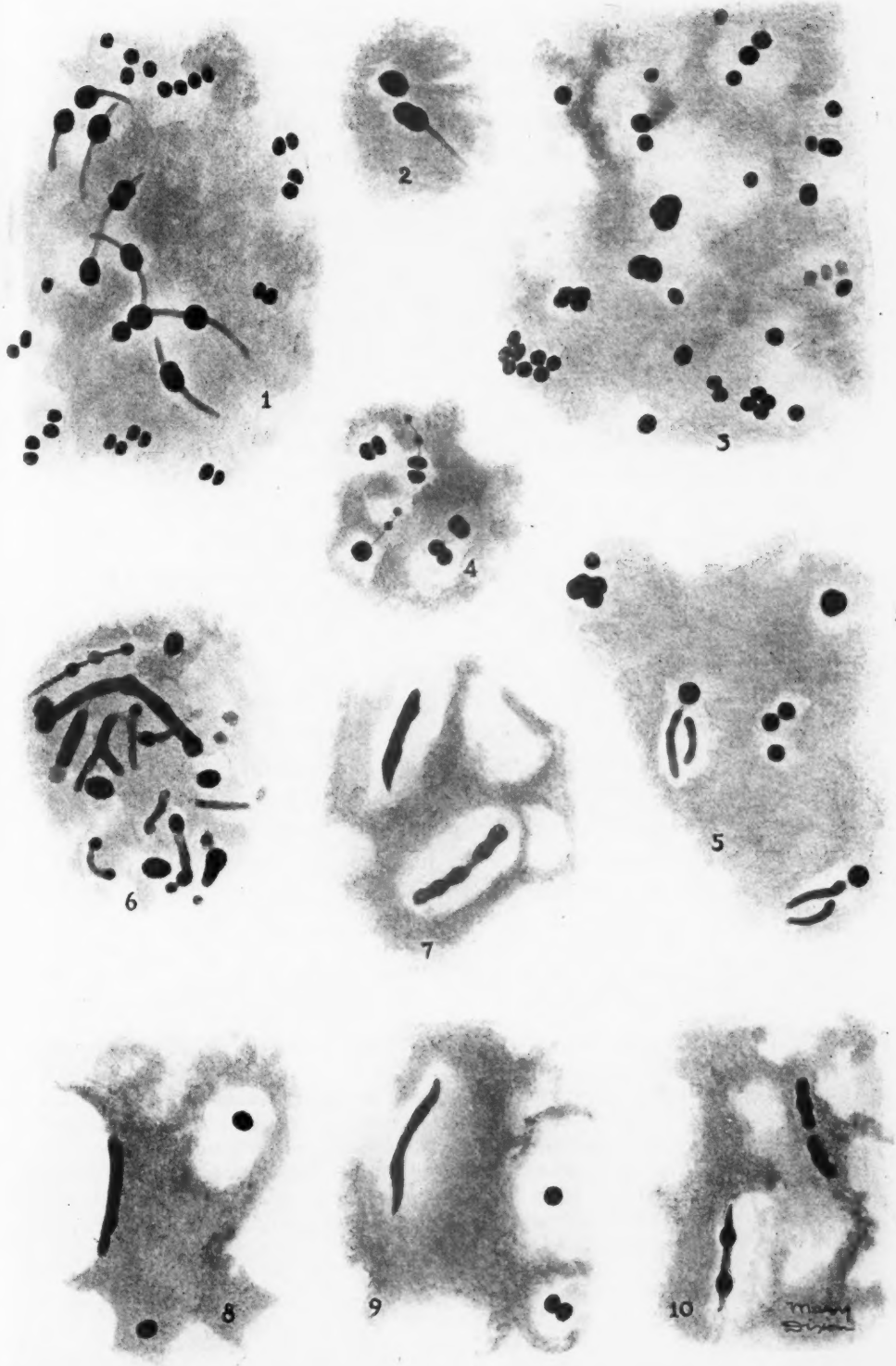
bacillary bodies attached. In plate 4, figure 3 is a photomicrograph of this drawing, and figure 4 is the same illustration with a red filter taking out all of the red color. Figure 2 is the same field as figure 1 of color plate II. Figure 1 is a smear directly from the lesion.

Most important of all was the result from single-cell cultures picked by means of the Janse-Péterfi[4] apparatus. After grinding the tissue in

[4] The Janse-Péterfi apparatus affords a means of picking individual microscopic particles in a moist chamber away from contaminating microörganisms. I have changed the moist chamber, so that a better working field is obtained for the pipettes. It consists of a cemented box, 1 x 1½ x 3 inches, with an opening at the top to accomodate a 1½ by 2-inch coverslip. The ends are closed by a rubber dam, through which the pipettes are permitted to operate. The picking pipette, operated by the right hand, should be as nearly 10 micra in diameter as possible. More than this makes the liquid flow too freely due to the decrease in capillarity. Less than this makes it too difficult to overcome the capillarity. The floor of the apparatus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a mortar, filtering through sterile gauze and finally through sterile cotton, centrifugating, washing and diluting to the desired concentration, five pickings were made of spindle-shaped microörganisms, each with single refractile granules, and planted on five media, namely, dextrose-bouillon, serum-bouillon, serum-agar, chocolate-blood-agar, and egg medium. One coccoid growth, arising after five days on egg medium, may have been from a degenerating tubercle bacillus. This coccus formed acid in dextrose, lactose, levulose, trehalose, and slightly in galactose and mannose, but no change in any other sugars. This result is unique, because the new form was a coccus and the microörganism picked out was one of the granulated bacilli. Two other growths, one in serum-bouillon and one in dextrose-bouillion, resembled the *Salmonella* group of microorganisms, but changed from generation to generation. The technique of picking single-cell colonies was controlled by making a large number of pickings of tubercle bacilli that did not grow: this is a control against outside contamination. Then another control was made, in which a certain number of rapidly growing colon-like forms were picked, and the colony growths checked against the number of microörganisms picked.

In general, the colonies that resulted amounted to about half of the number of microörganisms picked. Perhaps some of the latter were left in the pipette, while some may not have grown.

At the same time, a large number of cultures were made from the lung tissue, and a growth was obtained that resembled an atypical human type of tubercle bacillus culturally and pathogenically. The guinea pigs, inoculated with it, were no different than any other tuberculous guinea pigs. In rabbits it produced no tuberculosis at all, even in 1 mgm. doses, except for one or two isolated tubercles in the lung. Two chickens did not show any pathological changes upon inoculation.

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is overlaid with water, retained inside a dam of vaseline. This chamber is set into the clasps of an inverted mechanical stage operated by the left hand. The material for picking is diluted to the proper concentration and placed on the underneath side of the large cover-slip by means of the left pipette. Dilutions are made into smaller drops by the same pipette, until very few microörganisms are present in drops of about 25 micra in diameter. From these drops single pickings are made with the right-hand pipette, and all the microörganisms may be watched before and after the process, ensuring a single microörganism in the pipette. This microorganism is then deposited in a larger drop of sterile water, and this in turn is removed by a sterile hand-pipette to the culture tube. The capillarity is controlled by a mercury bulb held at a level to just balance the capillarity. The flow is regulated by raising or lowering the bulb by a foot-pedal. It requires considerable practice to perfect a technique, the details of which are too lengthy to give here.

However, the cultures did not produce the large granules that were found in the tissues; but smaller free granules were found.

Single-cell cultures of these granules, as well as the minimal infecting dose for guinea pigs, were attempted. Out of 14 pickings one tube produced a mould-like growth, resembling but not identical to that shown in

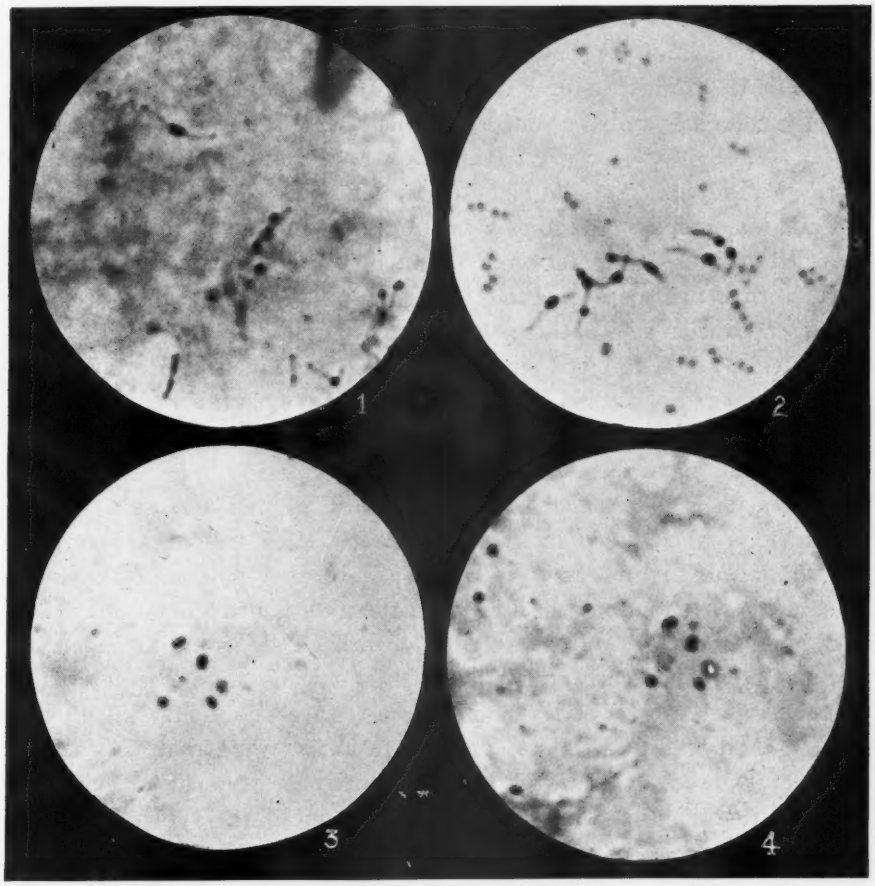

Plate 4

FIG. 1. Photograph of direct smear from lung of A175, showing granular forms of tubercle bacilli. × 2300.

FIG. 2. Showing degenerating granular forms. Granules enlarge and bodies disappear. Same as color plate II, figure 1. × 2300.

FIG. 3. Showing a group of granules in the bodies of disintegrated bacilli. × 2300.

FIG. 4. The same, except red filter was used, taking out the red granules (white) and exaggerating the blue (black). Same as color plate II, figure 4. × 2300.

figure 6, color plate II. This microörganism (culture 220) grows on solid media in a way that remotely resembles a culture of tubercle bacilli. It produced an atypical tuberculosis in guinea pigs, from which acid-fast bacilli were recovered: this will be described in a subsequent report. Six guinea pigs were inoculated with these granules: T57 received three, and T55 four granules: both were normal after two months. T53 received a bacillus with one large granule and three other granules; it died in 41 days of a peculiar type of pathological involvement. The lymph nodes, from the site of inoculation to the pulmonary hilum, were slightly enlarged, and contained pus with a few acid-fast bacilli. The spleen was slightly enlarged, but the liver appeared normal. The lungs were grayish-pink, and the right upper lobe was consolidated, with a caseous pneumonia containing a few faintly acid-fast bacilli. Sections revealed a diffuse proliferation of "epithelioid" cells in the consolidated part, with other more characteristic findings. The spleen contained foci of endothelial cells in the malpighian corpuscles.

Guinea pig T48 received six granules and was killed in 81 days. It presented more involvement like tuberculosis, but even this was markedly atypical. Perhaps, if the animal had been allowed to live longer, the process would have been still more like tuberculosis.

Guinea pig T49 received ten granules, and showed also an atypical tuberculosis when killed in 61 days. A few large tubercles were observed in the slightly enlarged spleen. Localized patches of caseous pneumonia were found in the lungs, and these contained a few faint acid-fast microörganisms and scattered endothelial cells, some arranged in groups resembling early tubercles. Other organs were characteristic of tuberculosis. In a series of 30 animals, with about fifty bacilli for dosage, there was a typical tuberculosis in all, showing that very small doses of granules or granular bacilli produced an atypical and chronic form of tuberculosis, while larger doses produced the typical disease. Perhaps small doses of bacilli would produce the same anatomical changes when an immunity develops before the microörganisms can produce overwhelming disease.

Another attempt was made to obtain a pure culture from the granules, and accordingly 14 more egg-culture tubes were seeded with one, two or four granules. Two growths of pure tubercle bacilli were obtained from four-granule plantings and one from a single-granule planting. This single-granule colony was an ordinary crateriform colony, about 2 mm. in diameter, when transplanted to other media. It has been kept grow-

ing ever since, and has remained pure to date (six months). There has been no return to the very large granular forms observed in the initial lesion, and no coccoid forms have come from the bacilli in salt solution.

In guinea pig S93, inoculated from the spleen of *S.W.* (autopsy 182), numerous dark red-blue granules were found in the usual organs, together with a few acid-fast microöganisms that had a "glassy" appearance. The bacilli take the acid-fast stain with difficulty, and appear to be like growing granules, that retain their heavy refractile coating, but have lengthened out into a bacillary shape. This is perhaps the non-acid-fast bacillary form described by Much.

Pieces of spleen were placed in sterile tubes, which were sealed inside a mason jar containing water and incubated. It seemed that, as hours passed, more acid-fast forms were observed. Up to 24 hours, and in reverse proportion, the dark granules seemed to disappear. Some appeared to pull apart and become acid-fast bacilli. After 48 hours the acid-fast forms took on another aspect, and in three days were as represented by color plate II, figure 6, when diptheroid microörganisms with acid-fast granules have appeared to develop. Numerous granules can be seen to have pulled apart, forming a short bacillus with acid-fast ends. No cultures grew on media after direct inoculation of the fresh spleen.

The spleen of S93 was macerated, and prepared for single-cell picking as in the preceding experiment, to see whether these forms would produce disease in guinea pigs. Guinea pigs, T52 and T56, which received five and two granules respectively, remained normal. T47 received a group of four to six granules, and died in 38 days, showing numerous granules and weakly acid-fast bacilli in foci in the lymph nodes and organs. Many granules were arranged in groups, as though held together by a matrix. There were only a fatty liver, a slightly enlarged spleen, and a congested lung with gelatinous pneumonia of one lobe. In this gelatinous portion were numerous epithelioid cells containing coccoid bodies. A retroperitoneal lymph node was reinjected into guinea pig T92, which lived 128 days. In this animal were a few small white tubercles on the surface of a slightly enlarged spleen. The liver was fatty, with a few tuberculous abscesses. The lungs contained localized patches of caseous pneumonia.

From guinea pig T35, inoculated from S92, a diphtheroid growth was obtained by incubating the spleen as before. Figures 7, 8, 9 and 10, color plate II, represent various stages of transition. The stain used for these microörganisms was a combination acid-fast and gram stain with a 20 per cent malachite-green as counterstain.

DISCUSSION

The point at issue is not the existence of the various types of granules, but to what extent they are concerned in the life cycle of the microorganism and the disease tuberculosis. The work of Mellon (28), Löhnis (29), Hadley (30), D'Herelle (31) and many others, appears to supplement that of the older scientists to the extent that all living microscopic forms (as well as the more evident macroscopic forms) of life undergo variations in their development. Quite naturally these changes are interpreted differently by the different workers, but all are in agreement concerning the variations.

If the granules of the tubercle bacillus play a rôle in the life cycle of the microörganism or in the secondary flora of the disease process, it is in harmony with biological laws. Regeneration of vitality by a change of generation and resting-stage formation is common in plant life. It is almost unnecessary to state here that living organisms vary. In fact, variation is one of the prime characteristics of life. Whether it takes place by mutation (DeVries) or by adaptation is immaterial. In either case the variation depends on the varying response of the germ-plasm to varying stimuli (environment) and the extent that these stimuli cause the vital processes to become diverted from the usual channels in reproduction. Whether acquired characteristics enter in, is of no moment in the present discussion. It is sufficient to know that life varies by gradual change, either by adding small increments from time to time by adopting fortuitous variations, or occasionally by more saltatory "mutations." The fact that living matter is plastic and will be altered or guided by changing stimuli, even of molecular magnitude, and that no absolutely identical stimuli exist in a complex involving living matter, affords the fundamental principles that have led to the establishment of the theory of variation into a law.

By methods of selective environment many of the higher forms of life have been changed into different forms in the course of a few years. The work of Burbank, although not performed in an accepted scientific manner, has been so vast and sweeping that the principles are clearly established. Now, what happens to larger plants in natural and artificial ways within relatively short periods of time can surely happen to microscopic plants, the life cycle of which is a thousand times less in magnitude of duration. Bacterial changes have been explained by different authors in different ways: as life-cycles (Löhnis); as variations

and mutations (Mellon); as dissociation (Hadley); and as mutations (D'Herelle and others). Perhaps there are elements of truth in all; but for the present it is sufficient to know that cultures of bacteria of all descriptions may undergo radical changes during their growth and decline.

We do not contend that these observations are new, for practically every phenomenon and experimental observation described in the preceding pages, except the changes to non-acid-fast coccoids, have been described by authors during the last forty years. It seems, however, that there has not been sufficient application made of this knowledge. While it is true that most of the disease "tuberculosis" can be accounted for by means of our present knowledge, the fact remains that these variations do happen and, if the complete biology of the parasite is to be known, we should study the microörganism from this angle. Furthermore, we should recognize in these changes, perhaps potential in every organism, an opportunity of dealing with the parasite in a more successful manner than we have in the past.

One characteristic, different from the ordinary life-cycle, is the random nature of the changes. Sometimes they seem to be atavistic. More commonly they appear to be a sort of vestigial remnant of a regular life-cycle. Fontes's discussion on the granules of bacteria is quite helpful in explaining changes that may occur in the granules. This author states that the granules are probably nuclear material mobilized in depots in the body of the bacillus, and this mobilization is quite variable from one to another. Likewise significant are the observations of Kirchensteins that these nuclear granules, composed of a different material than the bacillus as a whole, are capable of a separate existence.

When we consider that in this type of nuclear material lie the factors of hereditability, it is not difficult to understand the reasons for variations and mutations and the chaos that has existed in the taxonomy of higher bacteria. It is even possible that these changes may be of assistance in the problem of heredity.

There is a vast difference between the changes on artificial media and those in the animal body. The acid-fast bacillus, like many other bacteria, grows rather constantly for a while on artificial media. Finally, it begins to lose virulence, and then to undergo changes that render it only a saprophyte although it may still retain its tinctorial proclivities.

However, in the animal body, where the influence of the various antibodies and lytic substances are exerted upon it, the change in the parasite

is brought about in a shorter period of time and in a different manner. The microörganism is called upon to protect itself, and in doing this it manifests many tendencies to go through a life-cycle (or reveal atavistic tendencies) in perpetuating its existence, as it also develops toxic effects, or virulence, on the host. Any series of observations of tubercle microorganisms in the animal body will reveal the presence of many changes apart from the acid-fast stage. The changes are not alike in any two animals or, in fact, in any two organs. The general trend of the tuberculous process is to guide the growth of the germ along certain rather definite lines, depending on the reacting host and the action of this host on a microörganism that has in times past selected a certain slow mode of development to ensure its existence. When the environment varies too widely this average is departed from, and the result is an unusual manifestation. Rapidly growing forms that arise are either killed off by the host, or they may be slowly regenerated to the protected state as heavy-walled granules or wax-covered bacilli, passing through several stages of transition.

Kolle and others (32) have observed interesting phenomena concerning the transformation of paratubercle bacilli to a more typical form of tubercle bacillus. Herzog performed the reverse process by injecting mammalian bacilli into frogs and changed the bacilli into forms resembling pseudotubercle bacilli. It is much easier, however, to obtain variations with a microörganism known to be variable, in which there are forms that may be followed more easily. With one exception the microörganisms of this study have ultimately responded to the typical human type, although at the time of the first observation they were unusual in appearance. In certain environments these peculiar forms were capable of producing many anomalous growths when the reproductive bodies (granules) were actively stimulated during their sprouting period or *in statu nascenti*. At this time they appear to be in a state of flux, when slight changes of environment seem to exert the greatest effects.

We must bear in mind that there are two variables in the tuberculous infection, and that there is no way of predicting exactly the effect of one variable (the parasite) on the other (the host), and *vice versa*. By viewing the tuberculous infection in this light we may be able to understand better the variegated picture we get, not only in the parasite, but also the unusual effects on the host, as the parasite acts alone or symbiotically with other microörganisms.

SUMMARY AND CONCLUSIONS

A study has been made of the granules of the tubercle bacillus in tuberculous lesions in man and guinea pigs. No rule has been observed regarding the cause of granule-formation because the granules exist in apparently favorable environments, and do not exist sometimes in an unfavorable environment. Perhaps if the individual life of each microorganism could be followed, we should find that environment of an unfavorable nature causes it to seek protection in a resting state, or to undergo a "change of generation" for the perpetuation of its existence. Granules in certain stages of their life-cycle can be made to sprout and reproduce acid-fast microörganisms. They can, in other stages, be caused to sprout into actively motile bacilli that resemble certain young forms seen in bouillon cultures. These are non-acid-fast and motile. It is thought possible also that such forms may remain non-acid-fast in certain environments. Other granules apparently have been observed to degenerate into coccoid forms resembling *Staphylococcus tetragenus*. Others apparently go through a gonidiform stage, in which granules are held together in a matrix, and may sprout again in a way similar to the free granules. These granules are capable of producing tuberculosis in guinea pigs when picked out by the single-cell method. They are also capable of producing pure cultures of tubercle bacilli. A semi-acid-fast mould-like growth was also obtained having tuberculogenic properties, and ultimately regaining complete acid-fast properties on animal passage. Very small doses of granules produce atypical and chronic tuberculosis, while a typical form results from larger doses.

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THE FILTERABILITY OF THE TUBERCLE BACILLUS[1]

H. C. SWEANY

We are indebted to Fontes (1) for the demonstration of a filterable form of the tubercle parasite in 1910. The first inoculation of his filtrate produced only a local lesion, with hypertrophied lymph nodes and spleen. The cells did not contain bacilli but granules. Reinoculation into other guinea pigs produced a typical tuberculosis. Nothing further was reported until 1923, when Houduroy and Vaudremer (2) again demonstrated the presence of a tubercle-producing virus that passed through a Chamerland L3 filter. They grew tubercle bacilli on glycerine-potato medium, emulsified them, and filtered them at 10 to 15 cm. of mercury pressure. These microörganisms were weakly acid-fast, being decolorized by the usual methods, but not by chlorhydrateaniline. Valtis (3), early in 1924, filtered sputum through a Chamerland L2, and obtained a tuberculosis in the lungs with no intervening tuberculosis of the lymph nodes. Durand and Vaudremer (4) and Durand (5) obtained filterable forms that at first developed an atypical tuberculosis with an orchitis, but on animal passage a typical tuberculosis resulted. Valtis (6) repeated and confirmed much of the previous work and, in addition, observed that filtered sputum produced only an hypertrophy of the local lymph nodes that subsided quickly, but a swelling of the hilum lymph nodes, with hepatization of the lung, resulted later. Bezançon and Houduroy (7) and Arloing and Dufourt (8) repeated much of the work and confirmed previous statements. Dufourt alone (9) carried the work further, reporting on 30 tuberculous patients. The results of his guinea-pig inoculations fell into two well-defined groups: (1) wasting and death without tuberculosis, and (2) tuberculosis of the lymph nodes, with scattered tubercles.

Veber (10) found a filterable form of virus in a bacillus-free pleural exudate. Durant (11), with numerous experiments, proved the filterability of the tubercle parasite, and stated that the filterable form is on the borderland of visibility, and is not acid-fast and not culturable. Houduroy (12) states, and Arloing and Dufourt (13) and Calmette and

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others (14) have proved, that tuberculous virus will pass through the placentas of guinea pigs and infect the foetuses.

Valtis (15) found a rapidly fatal type of filtrate from a tuberculous lymph node of a child dying of tuberculosis. It killed one guinea pig in two days without producing any acid-fast microörganisms, and one in twelve days in which he found acid-fast microörganisms.

Valtis, Negrè and Boquet (16) found sufficient immunity conferred by a bacilliferous peritoneal filtrate to protect appreciably against a dose of 0.001 mgm. of tubercle bacilli in a guinea pig.

Fontes (17) in 1926 filtered several types of tuberculous material, and was again able to reproduce tuberculosis after several passages. Durand and his coworkers (18) described a curable form of disease produced by the tuberculous filtrate. Verdina (19) confirmed the filterability of the germ, and the inability to cultivate the filterable microörganisms.

Of great interest is the work of Couvelaire (20), who conducted observations on 357 foetuses of tuberculous mothers by injecting lymph-node and visceral products into guinea pigs. These animals did not develop tuberculosis, but acid-fast bacilli were found in the lymph nodes. This event confirmed the placental transmission of a tuberculous virus. Couvelaire stated that the congenital infection may be overcome, it may become latent, or it may produce disease.

Against the above array of work and results are the negative findings of Fessler (21) in 1926. This investigator was unable to duplicate any phase of the above-mentioned results,—a fact that is hard to reconcile with the numerous observations of others. It may be explained by the difference of filters, which are, after all, physicochemical membranes that depend upon the electric charge more than porosity. Again it may be that the emaciation type may have been overlooked.

EXPERIMENTAL

Various phases of this work were confirmed, and, in addition, the pathological changes were studied more in detail, special regard being paid to the type of cell-formation.

The pus from a closed Pott's abscess of a little girl, *J. T.*, was furnished by Dr. E. J. Berkheiser from his service at the Children's Memorial Hospital. A direct smear revealed only very small weakly acid-fast granules. Our cultures of egg medium grew a typical human form of tubercle bacillus as determined by animal inoculation. By direct ob-

servation of a dark-field preparation of the pus in salt solution we observed a *caput medusae* form of motile microörganism, which had been described previously (22). Filtration was performed through three patent Berkefeld filters that were proof against colon bacilli. After two hours in the incubator the coarse filtrate revealed many very small granules and sprouting bacillary forms. These forms were actively motile, faintly staining, gram-negative, and not acid-fast.

Each of these filtrates was injected into guinea pigs and cultured. The cultures were negative. Guinea pig P53, receiving 0.05 cc. on February 20, 1926, of the coarse filtrate, died February 25, 1926. The liver was mottled and yellowish; the spleen enlarged to twice its size and uniformly red; the lungs were congested, with consolidation in the upper lobes. Direct smears from the slightly enlarged hilum lymph nodes revealed very fine faintly acid-fast dust-like granules. After two hours in a salt-solution suspension very small motile bacillary forms and sprouting granules were observed. A pellicle grew on the salt solution in twenty-four hours, but no growth occurred when these lymph nodes were inoculated directly on culture medium. Cultures of a Salmonella-like microörganism were obtained from the salt solution that were discarded as contaminations, perhaps too hastily. A coarse Berkefeld filtrate was injected into guinea pig P94 on February 26, 1926, and it died April 12, 1926, of asthenia. Guinea pigs P96 and P97 were injected with macerated spleen of P53, and they also died of asthenia in about 60 days. Guinea pigs P93 and P94 were injected with a specimen treated with sodium hydroxide, and the same emaciated condition with death resulted.

The medium filtrate was injected into guinea pig P52 on February 20, 1926, and it died on April 12, 1926, with peculiar tuberculoid formations. The lungs were pneumonic (red hepatization), the liver contained a few whitish abscesses (not yellowish like the typical tuberculous abscess), the spleen was twice its normal size, but no acid-fast bacilli were found. When reinjected into guinea pig Q47 on April 15, 1926, this animal died on June 20, 1926, of a typical tuberculosis with acid-fast bacilli in all the lesions.

The fine "W" filtrate was injected into guinea pig P56 on February 20, 1926, and this animal died on April 12, 1926. The lungs were reddish, showing early congestion, and our record shows that there were no other gross anatomical changes except a marked emaciation. No further work was done on this animal.

A fresh aspiration of fluid was made on February 18, 1926, and guinea pigs P78, P79 and P92 were given filtrates intraperitoneally from the three filters as before. All died in about seven weeks in an emaciated condition. Direct inoculation of pus into P55, P54 and P57, in dosages of 0.01. 0.001 and 0.0001 cc. respectively, produced death with emaciation in about two months, but no definite tuberculosis was found.

The spleen of *S. W.* (autopsy 182) was macerated, and filtered through three Berkefeld filters as before, and each filtrate was injected into two guinea pigs on July 29, 1926. In about five weeks they all died during an epidemic, showing emaciation, fatty changes in the liver, and congestion of the lungs, but no tuberculosis. It seems possible that the epidemic was induced by the emaciation. The spleen of S12, dying after inoculation of a "medium" filtrate, was reinjected into S76, which developed hypertrophy of the hilum lymph nodes and a few scattered tubercles in the spleen. It died in three months.

The same type of filtration was performed on the lung of *R.R.* (A175), with results similar to those of A182.

The splenic tissue of A182, kept on ice for seven weeks, was filtered again and the injections were repeated. The reason for the repetition was because this patient had a generalized miliary tuberculosis following childbirth, when the tubercles and giant cells in the spleen contained dense blue-back coccoid granules instead of acid-fast bacilli.

The coarse filtrate, injected into T17, produced a slight enlargement of the spleen in seven weeks, with enlarged lymph nodes containing acid-fast bacilli, and death due to a gelatinous pneumonia; also, the medium filtrate produced in about seven weeks an asthenic condition, with a slightly enlarged spleen.

The fine filtrate injected into guinea pig T16 caused death in fifty-three days. The lungs were bright red, with areas of a dark red along the border. The spleen was enlarged to twice its normal size, the lymph nodes were only slightly enlarged, and the liver was normal. Microscopic examination revealed a slight proliferation of "endothelial" cells, with a thickening of the alveolar walls and atelectasis. The spleen showed passive congestion. There was nothing else unusual.

Material from the spleen, filtered through three filters, was again reinjected into 3 more guinea pigs, T62 (medium), T63 (coarse) and T68 (fine). The three guinea pigs became emaciated after two months and the local lymph nodes were enlarged. After four months the enlargement of the lymph nodes had disappeared, the guinea pigs had gained

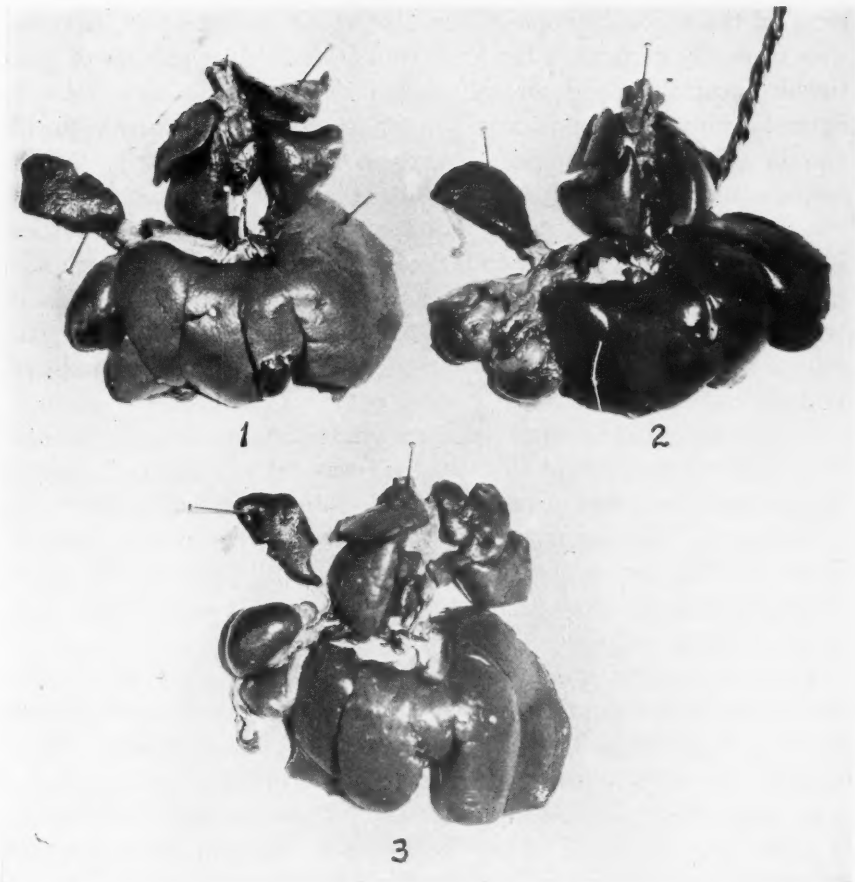

Plate 1

Fig. 1. Organs of T62, showing fatty scarred liver, with gelatinous pneumonia and enlarged hilum lymph nodes.

Fig. 2. T68, showing gelatinous pneumonia and enlarged hilum lymph nodes.

Fig. 3. T63, showing fatty changes of the liver and gelatinous pneumonia.

weight, and they appeared to be recovering. After six months they were killed and examined, and the lymph nodes were reinjected into other guinea pigs. T63 (plate 2, figure 3) showed no local lesion or enlargement of the regional lymph nodes; the hilum lymph nodes, however, were markedly enlarged. The lungs contained irregular patches of gelatinous pneumonia, and marked lymphoid hyperplasia (see plate 1, figure 1), with caseous pneumonia in one lobe. The liver was yellowish and the gall-bladder atrophic. The spleen was enlarged slightly. Microscopic examination revealed coccoid bodies in the spleen, liver and lungs. The spleen contained a few necrotic spots in the malphigian corpuscles, in which were observed a few epitheloid-like cells. The liver had marked fatty changes. In the lungs there was an extensive proliferation of lymphoid tissue. The consolidated portions contained numerous giant cells of the Sternberg type (see plate 1, figure 2) and a diffuse proliferation of "endothelial" cells.

In guinea pig T68 (given the medium filtrate) the pathological changes were quite similar, except that the liver was not so fatty and revealed several depressions that seemed to be healed abscesses (plate 2, figure 2).

Guinea pig T62 was not greatly different from the others (plate 2, figure 1). The next series injected from these still presented the hypertrophy of the lymph nodes and other features after six weeks. The study is still being carried on.

From the original spleen of T16 cultures were made on all common media, and a few slow-growing cocci, that would not grow when transplanted, appeared in the serum-bouillon tubes. A diphtheroid microorganism grew on a hog-spleen-agar culture tube. This diphtheroid was "purified" by single-cell picking, and the culture, when injected into 4 guinea pigs, produced an atypical tuberculosis, from which a typical tuberculosis resulted after the second passage and from which a typical human-like tubercle bacillus was recovered.

The interesting part of this observation is that, with the return of the characteristic anatomical changes of tuberculosis, the morphology and acid-fastness of the tubercle bacillus progressively returned. This will be reported in detail later. Only the filterable phase is emphasized here.

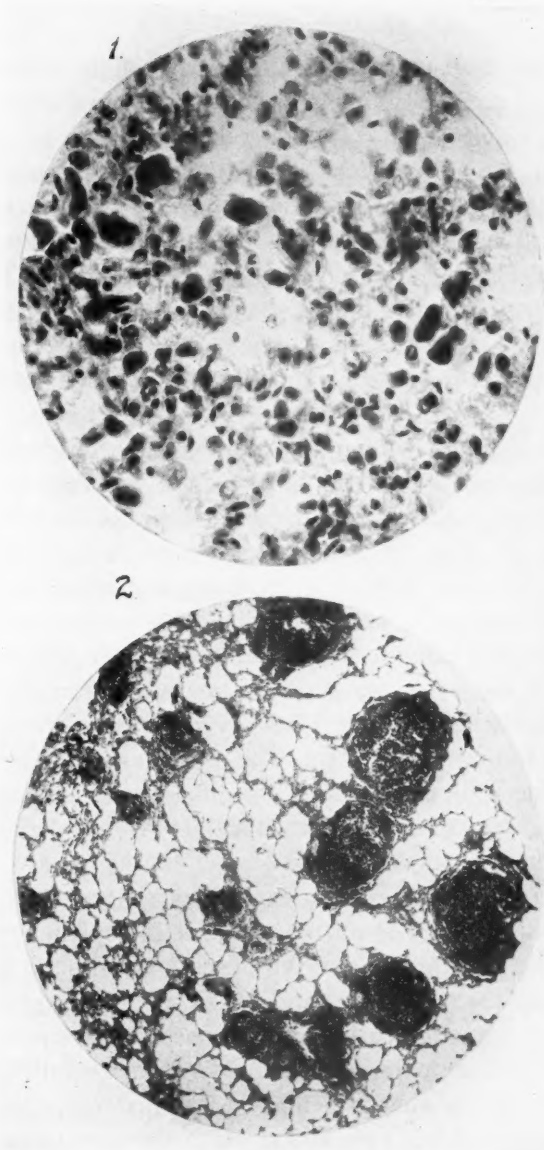

Plate 2

Fig. 1. Section of lung of guinea pig T68, showing Sternberg-Reed type of giant cells (× 412).

Fig. 2. Section of lung of guinea pig T62, showing marked hyperplasia of lymphoid tissue (× 45).

DISCUSSION

It seems evident that there exists a derivative of the tubercle bacillus that is capable of passing through the finest porcelain filters and still retaining degrees of virulence. This filterable form may be of decreased virulence, producing only a slight stimulation of the lymphoid elements and reticuloendothelial cells with recovery, or it may be such that a direct return to typical acid-fast bacilli will result at once or upon continued passage. Some filtrates are highly virulent, producing an early death, while others cause a belated death by emaciation.

Either of the two latter forms, I believe, may be produced by derivatives that are remotely related through a degenerative process to the tubercle bacillus.

It is possible that the nonimmune animal is more susceptible to these very small forms, and that, as the animal gains immunity, the infection is either overcome or the microörganism becomes protected by an acid-fast covering. In other words, these forms are less protected against immunizing bodies, due perhaps to their size and lack of covering. As a tentative explanation, let us suggest that in the process of reproduction or disintegration the tubercle bacillus forms granules of varying degrees of fineness from the very large blue-black (Much) granules to the very fine "symplasm" of Löhnis (23). A study of the large granules has been described in a former report (22). The "symplastic" or filterable type has been considered in this paper. The difference in activity of the two (if there is any) may be due to magnitude, as well as inherent virulence. The smaller the microörganism the greater the absorptive surface per weight of germ, and therefore the greater the activity and variation when this occurs. This theory is offered to assist in explaining the various types of reaction and difference in virulence. Besides this there are the variable host and the variable quality of the virus. Some granules appear to have a heavy refractile coating; others appear to have just a dense wall of the compact nuclear material, which under certain conditions of growth apparently secretes a mucoid semi-acid-fast material, that may be a feeble attempt at building an acid-fast wax. Others appear to be thinly walled "coccoids," that resemble chromatin bodies or nuclear material that has been extruded from their cells.

SUMMARY AND CONCLUSIONS

A virus exists in tuberculous lesions that is capable of passing through the finest Berkefeld filters and producing varying grades of disease in guinea pigs, depending on the particular virus. Some viruses produce an emaciation and death without any signs of tuberculosis when passed through one, two or three animals. Some are capable of regenerating a typical tuberculosis from which typical tubercle bacilli may be recovered. An atypical tuberculosis may result from the first filtrate, especially in that from the coarser filters, which, on animal passage, will also produce typical tuberculosis. During the process there seems to be a stimulation of the lymphoid tissue in the lungs and a progressive action on the reticulo-endothelial elements, producing in some animals giant cells of the Sternberg-Reed type, and approaching gradually the more typical anatomical formations of tuberculosis. This fact alone proves that some of the filterable forms are not tubercle bacilli, yet they possess sufficient intrinsic quality to regenerate tubercle bacilli on passage. It suggests also a relationship to lymphogranuloma.

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FURTHER STUDIES ON A NONPROTEIN TUBERCLE-BACILLUS ANTIGEN[1,2]

MAX PINNER

In a previous paper (1) the preparation of a purified antigen has been reported. It was obtained from the methyl-alcohol extract of tubercle bacilli which had been subjected to acetone, ether and chloroform extractions. It was purified by trypsin digestion and dialysis until the outer water did not contain any nitrogen; this procedure removed a considerable amount of nitrogen and all of the substances giving a positive biuret or ninhydrine test.

This product is a true antigen, since it readily produces complement-fixing and precipitating antibodies in normal rabbits, with which it reacts *in vitro* in a specific manner.

It was suggested that the antigenic action, both *in vivo* and *in vitro*, of this antigen is not attributable to a minimal protein contamination. Although it was not possible to rule out definitely the possibility of some protein admixture, the maximal amount of protein present must be very small, for the following reasons:

1. Its mode of preparation makes it highly improbable that it contains any considerable amounts of protein.
2. This antigen does not give any of the usual protein reactions which can be obtained with other tubercle-bacillus proteins up to a dilution of 1:5000.
3. Its nitrogen content is below 2 per cent.

Whatever the possible protein admixture may be, it is considered not to be responsible for its antigenic potency, for the following reasons:

1. The amount of tubercle-bacillus proteins, which contains the same amount of nitrogen as the alcoholic antigen used in immunization, is immunologically inert.

[1] From the Wm. H. Maybury Sanatorium (Municipal Tuberculosis Sanatorium, Detroit) Northville, Michigan.

[2] Read before the Pathological Section at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 25, 1927.

2. The amount of nitrogen contained in one antigenic unit of bacillary protein is 200 to 300 times larger than that in one antigenic unit of alcohol-soluble antigen under identical conditions.
3. Immune sera against this antigen do not bind complement with protein antigens, nor do antiprotein sera bind complement with the alcohol-soluble antigen. The same contingency holds good for specific precipitation.

TABLE 1

Antiprotein serum: Total nitrogen injected per 1 kg. body weight = 0.480 mgm.

	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048	1/4096	C.	
Purified antigen.....	++	+	+	−	−	−	−	−	−	−	−	−	−	Precipitation
Homologous protein	+	−	−	−	−	−	−	−	−	−	−	−	−	

	0.05	0.025	0.01	0.005	0.0025	0.001	C.	
Purified antigen.....	−	−	−	−	−	−	−	Complement fixation
Homologous protein....	++++	++++	++	−	−	−	−	

Antiserum: Alcohol-soluble antigen. Total nitrogen injected per kg. body weight = 0.240 mgm.

	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048	1/4096	C.	
Purified antigen..	++	++	++	++	++	++	++	++	++++	+++	+++	−	−	Precipitation
Homologous protein..	−	−	−	−	−	−	−	−	−	−	−	−	−	

	0.05	0.025	0.01	0.005	0.0025	0.001	C.	
Purified antigen.	++++	++++	++++	++++	++	−	−	Complement fixation
Homologous protein.....	−	−	−	−	−	−	−	

In table 1 are shown the titrations done on rabbit immune sera, obtained by injecting a tubercle-bacillus protein (Johnson's tuberculin fraction 304) and the purified alcohol-soluble antigen, respectively. The former substance was injected in such amounts that the rabbit received, per kilo of body weight, twice the amount of nitrogen as the one injected with the alcohol-soluble antigen. The protein antigen is definitely inferior in antigenic potency to the alcohol-soluble antigen; the respective immune sera are strictly specific.

In further studies, the following points received special attention:

1. Attempts were made to decrease further the nitrogen content of the product.
2. The antigen was studied in regard to anaphylaxis.
3. The relation of this antigen to the serologically active carbohydrates of the tubercle bacillus, Zinnser's residue antigen, was investigated.
4. The quantitative relation of the nitrogen content of different bacillary antigens to their serological activity was determined.

Ad 1: In the attempt to decrease the nitrogen content of the antigen without damaging its antigenic potency, careful use was made of the methods employed by Mueller (2) in the purification of the residue antigen. But all attempts were unsuccessful.

Ad 2: Active and passive sensitization of guinea pigs failed. It had been found in previous experiments, that in some instances reversed anaphylaxis could be produced in rabbits with some bacillary proteins with which active and passive sensitization of guinea pigs had been unsuccessful. The adoption of the method of reversed anaphylaxis in the present problem was of no avail. It may be further mentioned that an incubated mixture of antigen and homologous antiserum did not produce any toxic symptoms in guinea pigs which might have been referred to an anaphylatoxin.

Ad 3: Zinsser and Mueller (3) and Laidlaw and Dudley (4) isolated a complex carbohydrate both from culture broth and from tubercle bacilli. This so called ***residue antigen*** was found to be very active *in vitro*, but inert *in vivo*. According to Zinsser and his coworkers, this residue antigen is the only haptophore constituent of the tubercle bacillus. If this be true the alcohol-soluble antigen would contain the residue antigen, coupled with another substance, probably lipoidal in nature, which would add to the biologically inert residue antigen its antigenic potency *in vivo*. To prove or disprove this contention, two avenues of approach seemed to be practicable. First, it was to be determined whether the serological behavior of the residue antigen and of the alcohol-soluble antigen was at all similar. Dienes (5) has since published some experiments of this nature, which showed convincingly that the two antigens in question have materially different affinities for tuberculosis serum. In the present studies the completely purified residue antigen was not available. The experiments were made with a reprecipitated alcohol precipitate from an alkaline bacillary extract, that is, the same substance which Zinsser used in his serological work. The two substances were

titrated with the identical tuberculosis sera. In table 2 are shown the results with a serum from an artificially infected sheep. Similar titrations were made with a series of patient's serum; the results were quite comparable throughout. The residue antigen reacts much more weakly and much less frequently with tuberculosis serum in complement fixation than does the alcohol-soluble antigen, each antigen being used in the amount of one-fourth of one anticomplementary unit. In precipitation tests stronger and more frequent reactions were obtained with the residue antigen than with the alcohol-soluble antigen. Immunologically, then, the evidence on hand speaks against the identity of the haptophore groups in the two preparations. It remained to investigate the chemical identity of the two reacting substances. As seen from table 3 there is no parallelism between the amount of orcinol and α-naphthol positive substances on the one hand, and the serological activity, on the other

TABLE 2

Titration of tuberculous sheep serum

SERUM	0.05	0.025	0.01	0.005	0.0025	0.001	CONTROL
Crude alcoholic extract	++++	++++	++++	+	−	−	−
Purified antigen	++++	++++	++++	+++	+	−	−
Whole tubercle bacilli	++++	++++	++++	++++	++	−	−
"Residue antigen"	+	−	−	−	−	−	−
Saline (control)	−	−	−	−	−	−	−

hand, in whole tubercle bacilli and in the various preparations obtained in the process of purification. This observation would argue against the concept that the carbohydrates contained in the alcohol-soluble substance are the carriers of the serological potency. The complex carbohydrates, isolated by Zinsser and Mueller, are readily hydrolyzed by dilute mineral acids. This is apparently not the case with those in the alcohol-soluble fraction: by varying widely both the duration of the process and the concentration of the acid, it was never possible to obtain substances which would reduce Fehling's or Benedict's solution. Since these results were reported at the last annual meeting of the National Tuberculosis Association, it was found, however, that the hydrolyzed substance produces a positive test with Folin's blood-sugar reagents. This whole question is at the present time the subject of a more detailed investigation in our laboratory, the results of which will be reported in a future communication. The different solubility of the alcohol-soluble

antigen and of the residue antigen,—one soluble, the other precipitable in alcohol,—argues likewise in favor of their nonidentity, although this difference may be referable to the noncarbohydrate constituent in the alcohol-soluble antigen.

Ad 4: These studies were originally undertaken with the aim to add information to the question whether nonprotein substances could act as true antigens. It has not been possible to prove that the purified alcohol-soluble antigen does not contain any protein. The indirect evidence speaking in favor of the existence of a nonprotein antigen, has been

TABLE 3

	DRY WEIGHT PER 1 CC.	ANTI-COMPLEMENTARY UNIT	ANTIGENIC UNIT	ANTIGENIC QUOTIENT	NITROGEN		1 PER CENT SOLUTION	
					Per cent	Per antigenic unit	α-naphthol	Orcin
Tubercle-bacillus suspension	10.0	0.25	0.025	10	8.59	0.00215	++	+
	10.0	0.20	0.020	10	9.1		++	+
Methyl-alcohol extract	6.6	0.165	0.0066	25	4.61	0.000304	++	+
	10.1	0.101	0.0051	20	7.11	0.000355	+	+
Transferred to water	18.5	0.185	0.0046	40	4.82	0.000222	++	(+)
	80.0	0.200	0.0040	50	7.25	0.000280	+	+
Partly digested	9.6	0.12	0.0012	100	4.1	0.000049		
Completely digested and dialyzed	3.7	0.037	0.00037	100	1.86	0.0000069	++	(+)
	1.9	0.19	*0.00047*	*200*	1.63	*0.0000077*	++	+
Tubercle bacillus protein (Dr. T. B. Johnson), protocol no. 502		0.1	*0.01*	*10*	12.3	*0.00123*		

summarized above. Additional information could be expected by determining the quantitative relation between the antigenic potency of various bacillary fractions and their respective nitrogen content. It seemed of particular interest in this matter to consider the various intermediary products between whole bacilli and the purified antigen. In table 3 these data are assembled; the measure of the antigenic activity is the antigenic unit and the antigenic quotient. It will be seen that the preparations which are richest in nitrogen, that is, protein 304 and whole tubercle bacilli, have the largest antigenic units and the smallest anti-

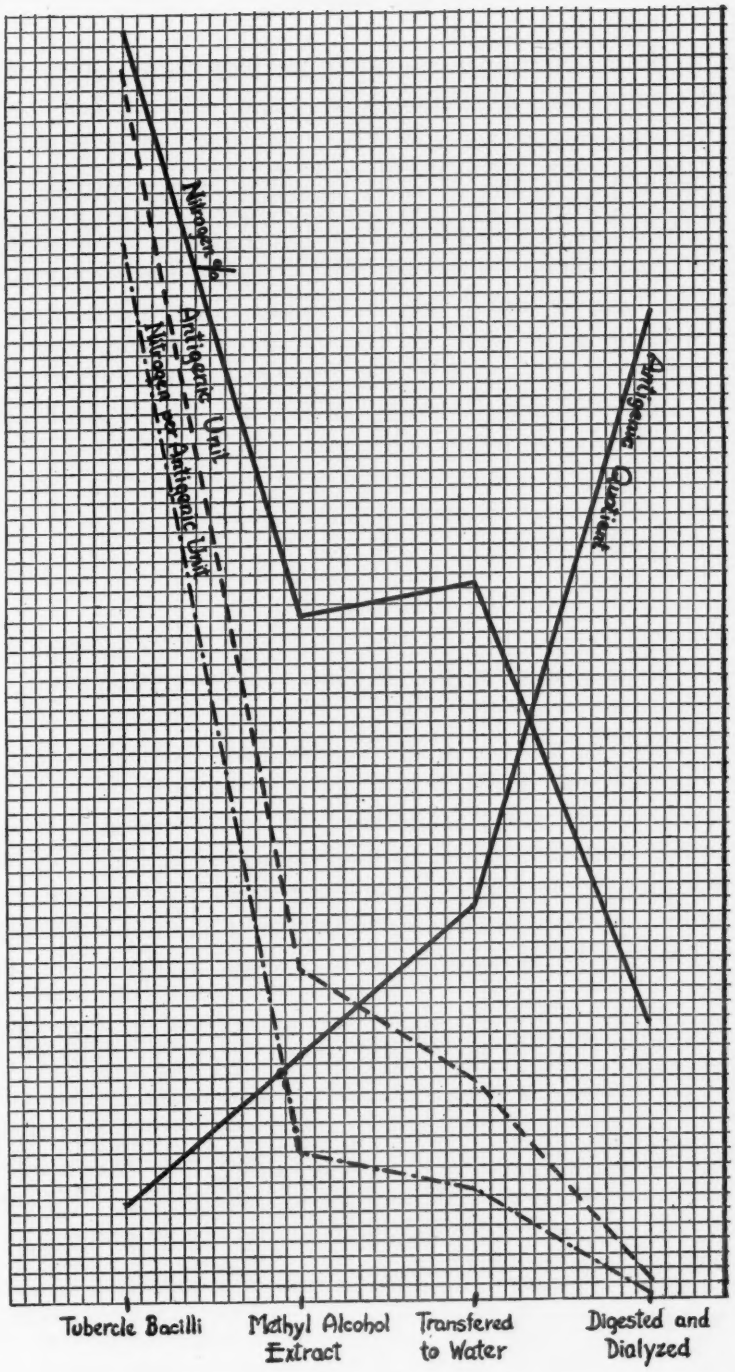
Nitrogen of Antigenic Unit
Nitrogen per Antigenic Unit
Antigenic Quotient
Tubercle Bacilli
Methyl Alcohol Extract
Transfered to Water
Digested and Dialyzed

CHART 1

genic quotients; that is, they are the least active antigens. As the nitrogen content decreases, the antigenic units decrease and the antigenic quotients increase; that is, the preparations are more antigenic. When these data are plotted in curves, as in chart 1, a quite remarkable parallelism is evident between decreasing nitrogen content and increasing antigenic potency. It is, of course, not possible to establish equally accurate measurements for the biological potency of the various preparations as for their serological activity. In numerous experiments, undertaken to compare quantitatively the antibody-producing power of the products listed in table 3, the results indicated clearly that the biological activity parallels closely the serological activity. This close parallelism between increasing antigenic strength and decreasing nitrogen content is presented as further evidence in favor of the view that the antigenic nature of the purified alcohol-soluble substance is independent of a possible protein admixture.

CONCLUSIONS

1. It was not possible to decrease the nitrogen content of the purified alcohol soluble antigen below 1.63 per cent without damaging the antigenic nature of the product.

2. This antigen did not produce anaphylactic symptoms under the stated experimental conditions.

3. Evidence is presented to show that the carbohydrates in the residue antigen and in the alcohol-soluble antigen are serologically different.

4. Studying whole bacilli, a purified protein fraction, and various intermediary products in the preparation of the alcohol-soluble antigen, a close inverse relation is found between nitrogen content and antigenic activity,

The protein fractions referred to were prepared by Dr. T. B. Johnson (*Amer. Rev. Tuberc.*, 1926, xiv, 164) and given to me by Dr. Wm. Chas. White, Chairman of the Research Committee of the National Tuberculosis Association. I wish to express my thanks for their support.

I wish to acknowledge my indebtedness to Dr. A. Wm. Lescohier, of Parke, Davis & Co., for providing me with large amounts of tubercle bacilli for this work.

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THE LOCAL IMMUNIZATION OF GUINEA PIGS AGAINST TUBERCULOSIS BY INTRACUTANEOUS INFECTION WITH TUBERCLE BACILLI OF LOW VIRULENCE[1,2]

GEORGE G. ORNSTEIN AND M. M. STEINBACH

Several years ago, while making an etiological study of lupus erythematosis, an opportunity presented itself to us to see many and varied cases of tuberculosis of the skin. One striking fact was definitely apparent: whatever the form and extent of the cutaneous tuberculosis in an individual, that patient seldom if ever had an active pulmonary lesion. In most instances the lungs were negative, but in occasional cases there was a minimal or fibroid tuberculosis. This fact was noted by Marfan (1) as far back as in 1886. Since that time we have considered the presence of a healed localized cutaneous or lymph-node tuberculosis as evidence of protection against pulmonary tuberculosis.

Among research workers in tuberculosis it has been suggested that, if one wishes to obtain the best skin reactions with tuberculin, the injection of tubercle bacilli should be made intracutaneously. This method of injection is said to increase the hypersensitiveness of the skin.

These observations, and the opinions of many concerning the importance of the skin as a factor in the production of antibodies and protective substances, led us to investigate the derma as a possible organ for the successful production of immunity against tuberculosis.

We considered whether or not this immunity to pulmonary infection could be explained in the following manner: The skin and mucous membranes seem to be closely associated in many diseases. The simultaneous appearance of eruptions over the skin and mucosae is an excellent example of this close association. The catarrhal bronchitis occurring during exanthemata is probably due to eruptions in the tracheobronchial mucosa. Even in syphilis, in the secondary stage, we frequently note the appearance of a catarrhal bronchitis. Myerson and Ornstein (2),

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[2] Presented before the Pathological Section, at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 26, 1927.

by means of a bronchoscope, have demonstrated it to be due to an eruption in the mucous membrane of the tracheobronchial tract similar to the more familiar one appearing on the surface of the skin.

It is probable, since the mucous membranes of the air-passages and the skin have correlative functions, that an immunity conveyed to the skin might protect the mucous membranes and *vice versa*. If this were true it would be no more than a manifestation of local immunity, as applied to the external coverings of the body, namely, the skin and mucosae of the air-passages.

Our first experiment was, therefore, an attempt to demonstrate a local immunity in the skin.

Our first problem was to find a microörganism which could produce a lesion resembling the healed tuberculosis of the skin or lymph nodes. We choose the *R1* strain of tubercle bacilli, which Trudeau had isolated in 1891, and which has been used extensively in this country in experimental work, particularly in tuberculoimmunity. Krause (3) claims for it a limited disease of the lymph nodes, and rarely a generalized tuberculosis. For our virulent strain we used the New York Board of Health strain *H305*, the lethal dose of which had been determined in our previous experiments.

INTRACUTANEOUS IMMUNIZATION AND INFECTION

Experiment 1: A group of guinea pigs was injected, intracutaneously, each with 0.1 mgm. of Old Tuberculin diluted 1 to 100. No skin reactions were noted. Guinea pigs from this group were used in the following experiments:

Six were then inoculated with 1 mgm. of R1 tubercle bacilli intracutaneously. The suspension was made up in physiological salt solution so that 1 cc. carried 1 mgm. of R1 tubercle bacilli. If any doubt arose as to whether the inoculation was intracutaneous the animal was discarded. Forty-five days later the animals were again tested with tuberculin in the same way as described above. They all reacted sharply. Sixty-six days following the immunizing inoculations of R1 tubercle bacilli, each guinea pig was inoculated intracutaneously with 1 mgm. of H305 tubercle bacilli, when the same care was exercised in seeing that the injection was always intracutaneous.

To control the experiment, 6 normal guinea pigs were also inoculated intracutaneously with 1 mgm. of H305 tubercle bacilli, while 2 normal

guinea pigs were then inoculated with 1 mgm. of R1 tubercle bacilli intracutaneously.

Two immunized animals died at 43 and 52 days after H305 infection. The remaining four were killed after the 106th day. The controls were killed over the same period of time.

Results

The Immunized Group: In the immunized animals no visceral tuberculosis was noted. The regional lymph nodes close to the site of inoculation were enlarged. Sections of the tissues were examined. Tubercles could be demonstrated only in the lymphatic structure. The liver, spleen, kidneys and lungs were normal. Tubercle bacilli were demonstrated in the lymphatic tissue after Ziehl-Neelsen's staining.

The Nonimmunized Group: In the nonimmunized group visceral tuberculosis was demonstrable microscopically in the stained sections. In the two animals used as controls for the R1 tubercle bacilli no visceral tuberculosis was demonstrable macroscopically or microscopically. The lymph node nearest the site of inoculation was enlarged, and tubercles and tubercle bacilli were demonstrated in sections of it.

We may conclude from the above experiment that intracutaneous immunization protected guinea pigs against visceral tuberculosis for a period of 106 days. The following questions then arose:

Is this method of immunization a lasting one? Is it a form of local immunity? Will intracutaneous immunization protect in a similar manner against infection through paths other than the skin?

Experiment 2: In order to determine the duration of this form of immunity, experiment 1 was repeated.

Twelve guinea pigs were used in each group. All were given preliminary tests with tuberculin, when no skin reactions were noted.

Twenty-four guinea pigs were inoculated, intracutaneously, with 1.0 mgm. of R1 bacilli, and they all reacted sharply to tuberculin two weeks later.

Seventy days following the immunizing inoculations 12 of the guinea pigs were inoculated intracutaneously with 0.1 mgm. of H305 bacilli. It was thought best to use a smaller dose of the virulent germs than had been used in experiment 1.

At the same time 12 normal guinea pigs were injected in a similar manner with the same dose of H305 bacilli.

The remaining 12 immunized guinea pigs were left untouched. They were to be used for observing the character and course of the infection with R1 bacilli.

Results

The Immunized Group: The guinea pigs in this group either died or were killed in from 61 to 374 days following the virulent infection with H305 bacilli.

The first evidence of visceral tuberculosis appeared in a guinea pig 91 days after infection with H305 tubercle bacilli. The animal was killed and the autopsy revealed the following:

The right inguinal lymph nodes were enlarged (the intracutaneous infection had been on the right side). The left inguinal lymph nodes also were enlarged. A solitary tubercle about the size of the head of a small pin was noted on the surface of the liver. It was whitish, and penetrated slightly below the surface of the liver. The spleen and lungs were normal.

The next occurrence of visceral tuberculosis was observed 155 days following infection with H305 bacilli. This guinea pig had more tuberculosis than the preceding animal. On the surface of the liver two small tubercles were noted. The spleen was tuberculous, but the lungs were normal. The inguinal lymph nodes on both sides were enlarged and hard. The guinea pigs next killed were free from visceral tuberculosis until the 267th day. The animal killed at that time had a few tubercles in the liver and spleen, while a few tubercles were also seen in the left lung. The last animal was killed on the 374th day. Its spleen had a few scattered tubercles, but the liver and lungs were normal.

One animal was lost. Out of the eleven, 7 escaped visceral tuberculosis from periods varying from 61 days to 233 days.

The Nonimmunized Group: In this group the length of life after infection was from 61 to 377 days. Three guinea pigs died of tuberculosis, the first 212 days after infection. All the organs except the kidneys were involved with massive necrotic lesions. The second guinea pig died 251 days and the third 267 days following H305 infection.

At the autopsy of the animal killed 61 days after infection, two small tubercles were demonstrated in the liver, but the spleen was covered with many fine tubercles. The lungs were normal. Both inguinal and the right axillary lymph nodes were enlarged.

The animal killed as a control to the immunized guinea pig, which had a single solitary tubercle at the surface of the liver after 91 days of infection, had miliary tuberculosis of the liver and spleen. The lungs were not involved. All the lymph nodes were involved, especially the inguinals.

The animal killed as a control to the immunized guinea pig after 155 days of infection had extensive tuberculosis. The spleen was massively involved, the liver covered with fine tubercles; and the right inguinal and retroperitoneal lymph nodes were also tuberculous. This was in contrast to the two tubercles found in the liver and the moderate tuberculosis in the spleen of the immunized animal.

In all these control animals, from 61 days to 377 days after infection, there was demonstrable evidence of visceral tuberculosis; and the extent of the tuberculosis was in marked contrast to the tuberculosis noted in the nonimmunized animals.

The R1 Control Guinea Pigs: To our surprise, 5 out of the 12 guinea pigs used as controls of the immunizing dose developed visceral tuberculosis. The 12 animals were inoculated with 1 mgm. of R1 bacilli intracutaneously at the time the other 12 animals were immunized. The animals were killed three at a time,—one immunized, one nonimmunized, and one R1 control.

The first animal in which tuberculosis of the organs was noted was killed 61 days after infection with H305 in the first two groups of guinea pigs. The time which elapsed since the R1 injection was 101 days. Two suspicious areas were noted on the surface of the liver. They looked like very fine tubercles. Sections of the liver were normal, but it is possible that the two tubercles were not in the cut sections. Tuberculosis occurred in the other 4 guinea pigs 251, 305, 354 and 384 days after infection with R1 bacilli; although the amount of the visceral tuberculosis was very slight, and in these 4 animals it was difficult to demonstrate tuberculosis in the histological sections. Two guinea pigs were killed as late as 378 and 414 days after infection without any demonstrable tuberculosis in the organs.

Summary

We can conclude from the above experiments that immunization through the intracutaneous route delays visceral tuberculosis. And we can now answer the question as to whether it is lasting. It apparently is not. Infection of the organs occurs as time elapses, but because of the happenings in the R1 control group, it is difficult to judge whether the visceral infection in the immunized group is due to R1 or H305 infection. It is possible that it takes that length of time for R1 infection to develop in the organs. As much visceral tuberculosis occurred in the R1 controls as in the virulent-injected immunized group, and we were unable to determine whether it was due to H305 or R1. The next step was to investigate whether this form of immunization will delay infection through other routes than the skin.

INTRACUTANEOUS IMMUNIZATION AND SUBCUTANEOUS INFECTION

Experiment 3: Thirty-six guinea pigs were tested with tuberculin, without skin reactions. They were divided into three groups of 12 animals each.

Twenty-four were immunized, intracutaneously, with 1 mgm. of R1 tubercle bacilli. Forty days later they were again tested with tuberculin. They all reacted sharply. One group of twelve was left as a control group; the other group was injected subcutaneously with 0.1 mgm. of H305 tubercle bacilli.

Results

The Immunized Group: Forty-three days after intracutaneous immunization with R1, 12 guinea pigs were inoculated subcutaneously with 0.1 mgm. of H305 tubercle bacilli. The first was killed 69 days after infection, when several small discrete tubercles were seen in the liver and a few in the lungs.

The next animal was killed 104 days after infection. The left inguineal lymph nodes were enlarged (H305 had been injected in the left groin). The lungs and spleen were normal, but many fine disseminated tubercles were spread over the surface of the liver.

One of the animals died of lobar pneumonia 109 days after infection. In this animal there was no evidence of tuberculosis except for an enlarged right inguinal lymph node.

Three guinea pigs died 163 days after infection, two of lobar pneu-

monia, that also had tuberculosis of the liver, spleen and lymph nodes. The cause of death of the other animal was not determined, but tubercles were seen in the liver and spleen. Another guinea pig, killed during this same period, showed evidence of tuberculosis.

One animal was killed 195 days after infection, and was found to have no tuberculosis except for a right inguinal lymph node the size of a large pea. The next animal killed (216 days after infection) had one small tubercle in the liver, which was not demonstrable in the histological sections, while the last one killed (272 days after infection) had no tuberculosis.

Four of the ten guinea pigs were free from visceral tuberculosis, while the remaining six had macroscopic tuberculosis. In two of this latter group we were unable to confirm the tuberculosis histologically. The first two animals, which died 6 and 10 days after infection, were not included.

The Nonimmunized Group: This group of normal guinea pigs was inoculated subcutaneously with 0.1 mgm. of H305 tubercle bacilli on the same day as the immunized animals were similarly treated with H305. The dose was the same as that given the immunized group. Two of the animals were lost. Of the remaining ten, 5 died of tuberculosis and the other 5 were killed and found to have tuberculosis in the liver and spleen. One guinea pig, dying within 36 days, had a gram-positive-coccus infection and tuberculosis of the liver. The next death occurred 54 days after infection, in an animal with extensive tuberculosis of the liver, spleen and lungs. The first of the other ten animals was killed 69 days after infection. It had massive tuberculosis of the liver and spleen, with a few tubercles in both lungs. The last of these animals was killed 252 days after infection. Its lesions were extensive, and in most instances massive. In only one guinea pig, killed 216 days after infection, was there a lesion which resembled those in the immunized guinea pigs: two small tubercles were noted in the liver and the spleen was also tuberculous.

The R1 Controls: We were again surprised to note the appearance of visceral tuberculosis in 6 guinea pigs. This occurred 206, 219 (two animals), 257, 268 and 295 days after infection with R1 bacilli. The extent of the involvement was usually a few tubercles in the liver or spleen.

SUBCUTANEOUS IMMUNIZATION AND INFECTION

Experiment 4: Thirty guinea pigs were divided into three groups of ten each. Two groups were immunized with R1 bacilli subcutaneously, after which one of these was injected subcutaneously with the more virulent H305 bacilli. The remaining group of normal guinea pigs was similarly injected subcutaneolusly, with dosages of R1 bacilli, 1 mgm., and of H305 bacilli, 0.1 mgm.

Results

The Immunized Group: Two animals died 6 and 10 days after infection with H305. The first had pneumonia with a purulent pleural effusion; and its liver contained many fine tubercles, its spleen many fine and large tubercles, and all its lymph nodes were involved. Its death was due to tuberculosis. This massive tuberculosis could only be explained as a result of the R1 injection. The animal died 50 days following the ubcutaneous injection with R1 tubercle bacilli. The cause of death of the other animal could not be determined. Two more animals died 31 days after infection. The cause of their death was not determined, but both had tuberculosis of the liver and spleen. Another guinea pig died after the 100th day from extensive tuberculosis of the liver, spleen, lungs and the lymph nodes. The 101st day claimed another animal with tuberculosis of the lungs, spleen, liver and lymph nodes. One guinea pig was killed 136 days after infection. This was the only one of the immunized group which did not develop visceral tuberculosis. The remaining two guinea pigs were killed 227 and 230 days after infection: both had tuberculosis of the liver and spleen. One guinea pig was missing.

The Nonimmunized Group: Five of these animals were lost. Tuberculosis was demonstrated in the guinea pigs at from 76 to 230 days. Its extent varied from a few tubercles to massive involvement.

The R1 Controls: Two animals died within the first month. Of the remaining eight, 4 developed visceral tuberculosis and 4 remained free of infection. Of the four that remained free from visceral tuberculosis, 3 died of paratyphoid infection about 83 to 87 days after infection. The fourth animal was killed on the 243rd day. The four in which visceral tuberculosis was demonstrated were killed on the 181st, 243rd, 244th and 251st days after infection.

DISCUSSION

In experiments 1 and 2 (intracutaneous immunization and intracutaneous infection) 4 out of 17 animals developed visceral tuberculosis. A few tubercles were seen on the surface of the liver or the spleen. The tubercles were fine and small in size. In 2 guinea pigs we were not able to corroborate our macroscopical impressions in our histological sections. This may be due to the fact that sections of normal liver and spleen were cut because of inability to see in the fixed tissue the one or two fine tubercles.

In the intractuaneous immunization and subcutaneous infection only 4 out of 10 guinea pigs were free from visceral tuberculosis. In the six in which tuberculosis developed there was a marked contrast in the extent of the lesion as compared with the nonimmunized animals. The immunized animals had only a few tubercles, and in two of the six we were again unable to corroborate the tuberculosis in the histological sections.

We may account for the greater protection in the skin-infected animals by assuming that we produced a local immunity in the skin. The protection was the same in both the animals reinfected on the side where they were immunized and in those immunized on the opposite side. We also considered a mechanical factor; that the bacilli encountered greater difficulty in escaping from the derma than from the subcutaneous tissues. This factor can be eliminated because the extent of the lesion in the intracutaneously and subcutaneously infected nonimmunized guinea pigs was about the same.

It is interesting to note that in the reinfections there were the usual manifestations of inflammation as described by Krause and Peters (4). There was every shade, from a most transient and slight inflammation to one that was most violent and rapidly necrotizing and haemorrhagic. All ulcerations healed completely.

Similar observations of this form of intracutaneous immunization against intracutaneous infection have been reported by Roemer and Joseph (5). They concluded, after some measured doses, that amounts below 1,000 bacilli were well resisted in the skin, but that occasionally infection was produced by more. Kraus and Volk (6) also reported favorably on intracutaneous immunization against intracutaneous infection. They immunized apes by scarifying the skin with small doses of virulent tubercle bacilli. This immunization protected the animals

against repeated inoculations in a similar manner. The immunity did not hold when avirulent microörganisms were used for immunization.

When we compare intracutaneous with subcutaneous immunization, we begin to see definitely the importance of the skin as a factor in immunization. Only one of the subcutaneously immunized group escaped visceral infection. The extent of involvement, though a little less, began to take on the appearance of that in the controls. The comparison of these two experiments made us consider other possibilities besides local immunity in cutaneous immunization. We cannot speculate on what they may be at the present time.

It can readily be seen that R1 tubercle bacilli can produce visceral infection. Baldwin and Gardner (7) had a similar experience when their guinea pigs were made to inhale R1 bacilli. Perhaps we used too large a dose. We believe that some of our visceral infection in the intracutaneously immunized group is due to R1 instead of H305. Unfortunately, we did not think of checking it by reinoculating some of the infected tissue into normal guinea pigs, as did Baldwin and Gardner (7).

CONCLUSIONS

1. Intracutaneous immunization confers a considerable degree of protection against intracutaneous reinfection with tubercle bacilli.
2. Intracutaneous immunization confers a lesser degree of protection against subcutaneous reinfection.
3. Intracutaneous immunization confers a greater degree of protection against reinfection than does subcutaneous immunization.

We wish to express our appreciation of the helpful suggestions of Dr. Frederick P. Gay, and of the encouragement and stimulus received from Dr. James Alexander Miller, and also of the technical assistance of Dr. Joseph Alexander.

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INNATE RESISTANCE TO TUBERCULOSIS[1]

CHARLES T. RYDER

The purpose of this paper is to call attention to a group of familiar facts, which in their relation to one another seem to the writer to make it improbable that acquired immunity is an important favorable factor in human tuberculosis, and probable that "natural," innate, or hereditary immunity is a very important one.

The tubercle bacillus must still be regarded as a universal virus. Universal viruses are those which are so widely disseminated in the human environment that everyone born into it is practically certain to encounter them. The nearer a virus comes to being ubiquitous, the earlier in life will infection with it tend to occur. If, as in the case of measles, for example, infection, illness, and recovery are followed by a marked and prolonged specific increase of resistance, that is, an acquired immunity, the disease in question becomes known as a children's disease. It may be stated as a general principle that every disease whose virus is constantly present in the social human environment, and in which first infection is unquestionably followed by an effective acquired immunity, has its highest death-rate in the first decade of life, that is, in the period of first infection.

Of all those exposed to a disease and infected, a certain proportion will have sufficient innate resistance, so that they will develop no symptoms. A certain proportion will have so little innate resistance, or will be subject to such unfavorable conditions overwhelming their resistance, that they will succumb. The rest,—the majority in the case of some "children's diseases,"—show symptoms of invasion and conflict with the parasite, but their innate resistance is sufficient to effect recovery even on first infection, and is as a rule markedly increased for the rest of life.

Theobald Smith in his presidential address to the National Tuberculosis Association in 1926 emphasized the importance of innate or hereditary immunity, and the fact that "acquired resistance is only a specific increment of natural resistance." Of course, if the power to resist disease were not an inherited characteristic, first infections with virulent

[1] From the Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado.

microörganisms would always be fatal, and there could be no such thing as acquired immunity,—a condition occasionally observed, as in pneumonic plague and some epizootics. This truth, so obvious once it is stated, and applicable to all diseases, is too often ignored in discussions of immunity, especially in tuberculosis.

We have, then, as a characteristic of all common infectious diseases the fact that most exposed persons do not die, but either escape or recover. We have the further fact that, if the virus is generally distributed and if recovery is followed by effectively increased immunity, the curve of death-rates by age-periods will have its peak in childhood and a low level for the rest of life.

Now how does tuberculosis compare with such diseases? It is reasonably certain that nearly everyone in contemporary civilized life with its urbanization and free communications is exposed to the virus in early life. There is a vast amount of evidence both from tuberculin tests and, what is more convincing, from autopsy studies, that a high percentage of children suffer actual invasion by the tubercle bacillus, with lesion, and that of these lesions of first infection the great majority heal. So far tuberculosis behaves like the children's diseases described, but here the resemblance ceases. For individuals who have had these entirely successful first bouts with the bacillus do not appear to be less likely than others to develop fatal tuberculosis in later life. In fact the progressive pulmonary tuberculosis which is responsible for most of the deaths from the disease is regarded by all, even those who feel that acquired immunity is an important favorable factor in tuberculosis, as a secondary (or secondary-tertiary) lesion. Whether it results from extension or reinfection, it is at least not a lesion of first infection, but one characteristic of the "immunized" or sensitized individual. And the death-rate, far from being high in the age-period of first infection and low afterward, as in the diseases followed by acquired immunity, is very low in the period during which we are acquiring "primary complexes" and positive skin tests, and high throughout the age-period after we have become "immune."

I have drawn the curves of deaths by age-periods in the United States Registration Area for 1923 for measles and whooping cough—ubiquitous and immunity-conferring diseases,—and for influenza and lobar pneumonia, both of which seem to approximate the status of universal viruses (chart 1). Note that the more effective the acquired immunity characteristic of a disease, the more strictly are the deaths from that disease

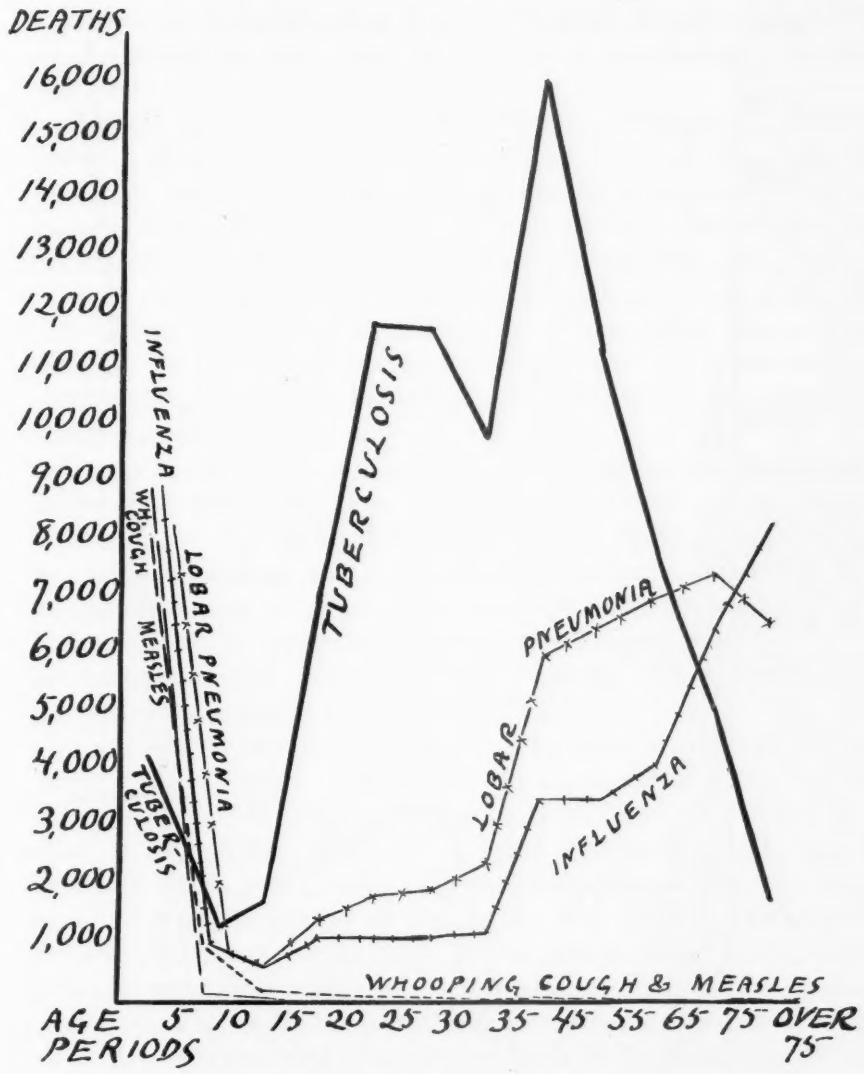

CHART 1

These curves, based on the mortality statistics of the United States Registration Area for 1923, indicate the deaths by age-periods from five infectious diseases to which nearly everybody is exposed. In diseases like measles and whooping cough, which are followed by a marked increase of immunity—acquired immunity—the deaths occur chiefly in the first years of life, the period of first exposure. In diseases in which acquired immunity is not a prominent factor, such as influenza and lobar pneumonia, there is no such distribution. In tuberculosis the lowest mortalities coincide with the period of first infection, judged by skin tests and autopsy data. Throughout later life the rates are high, showing that the first infection, successfully combated, is not followed by an effective immunity.

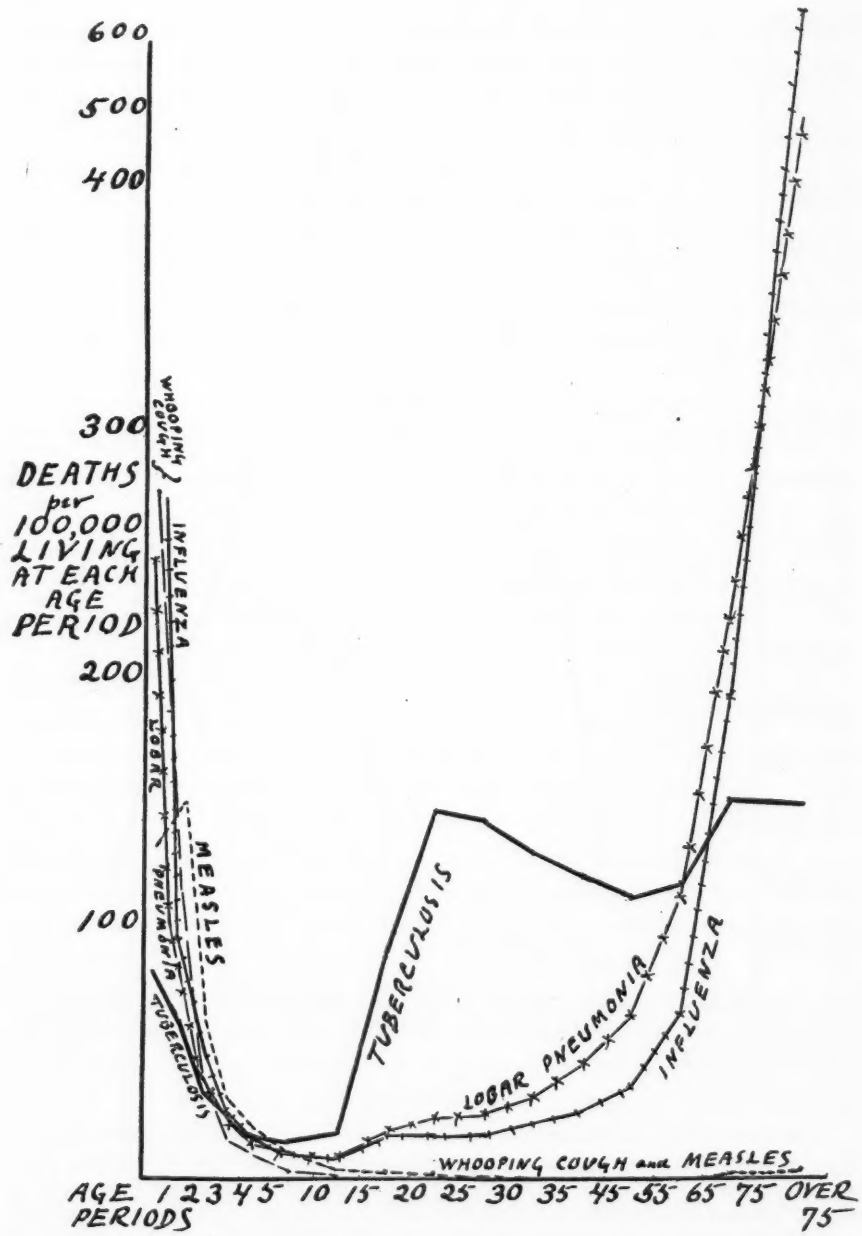

CHART 2

Here the data presented in chart 1 are rearranged to show death-*rates* by age-periods, including the rates for each of the first five years of life. Note the very low rates for all diseases between infancy and adolescence, and the sustained high rates for tuberculosis throughout adult life.

concentrated in the first years of life. These are of course simply two ways of saying the same thing, granted that early infection is virtually universal.

Against these curves I have drawn that for tuberculosis. Nothing could be more striking than the contrast between this curve and the curves for measles and whooping cough, diseases in which acquired immunity, while not absolute, is an effective reality. The tuberculosis curve resembles more those for influenza and lobar pneumonia, diseases in which the resistant phase following an attack is very limited; but the high mortality throughout adult life is even more marked than in these diseases. In chart 2 I have rearranged the data to show death-*rates* per 100,000 living at each age-period, each of the first five years of life being shown separately.

Data of this kind, secured from various sources, always seem to be in fundamental agreement. The slopes of the curves vary, but their form is characteristic. For comparison I have drawn curves for measles, whooping cough, diphtheria and scarlet fever (the latter two probably less ubiquitous viruses) and tuberculosis, from material kindly supplied by the Metropolitan Life Insurance Company from the company's industrial mortality experience. The curves drawn are for 1920. Those for the preceding nine years are practically identical.

A possible interpretation of the facts pictured by the tuberculosis curves is the following: That *primary* tuberculosis really is like the children's diseases; that first infection comes earlier than we have supposed, chiefly in the first five years of life; and that there is a resultant acquired immunity which lasts through childhood and disappears later, perhaps with the complete healing of the lesion. This attractive hypothesis however seems to be contradicted by the skin test and autopsy data, which show that only a minority become infected in the first five years of life, and the majority in the next fifteen years from five to twenty. The possibility of spontaneous vaccination without skin sensitization or demonstrable lesion is one upon which we have no evidence.

Moreover it seems gratuitous to assume any specific increase in immunity to tuberculosis in the period between infancy and adolescence, in view of the fact that the death-rates for all diseases are low in this period. (See chart 2.) In the case of each disease there is a high rate in the first two years, which, as has been emphasized in discussions of tuberculosis in infants, can be largely accounted for by the infant's dependence on others and consequent close contact,—sometimes almost marsupial in

its intimacy,—with infectious adults. This, moreover, is no doubt the period of elimination of those whose innate mechanism of resistance is

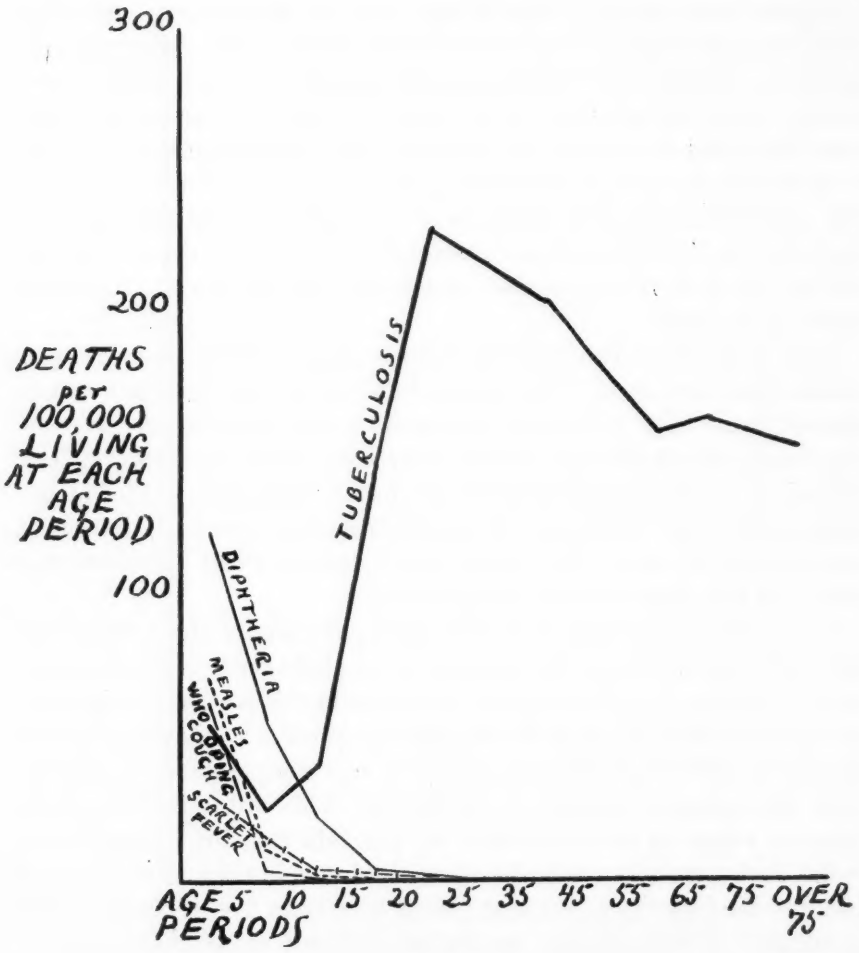

CHART 3

This graph, based on the industrial mortality experience of the Metropolitan Life Insurance Company for 1920, shows that data from different sources (in this case somewhat selected material) yield curves which differ in detail, but keep the characteristic form for tuberculosis on the one hand and for the immunity-conferring diseases on the other. This is true of the curves drawn from the same material for each of the nine preceding years.

least competent, or is overwhelmed by unfavorable circumstances. It is tempting to imagine that in some instances the functions of resistance,

though hereditary traits, are incompletely developed at birth, as is the case with eye-color and resemblance to a parent. But this assumption is hardly necessary in view of the increasing number of reports, especially from the French, of infants *already infected* by tuberculous mothers, who have made good recoveries when removed to sanitary surroundings. The heart-breaking dogma that babies have no resistance to tuberculosis seems pretty well disposed of.

The low death-rates from all causes in childhood offer a fascinating problem in immunology, and the phenomenon suggests Theobald Smith's hypothesis of the exhaustion of a limited innate supply of resistance, to which I shall refer again later.

It may be said that the comparison of chronic and acute diseases is fallacious, and I would not force the analogy. The whole mechanism of resistance may be entirely different, though among newly exposed races tuberculosis tends to be an acute disease. All I would assert the curves to show is, first, that children of our races have a high resistance to first infection with the tubercle bacillus as well as to all other common diseases; and, second, that there are diseases in which first infection is followed by an effective increase of resistance, a considerable security against death from the same disease in later life, and tuberculosis is not one of them.

Recognizing, as we must, that children of civilized stock resist their first tuberculous infection extremely well, how are we to explain the fact? The evidence seems to me to lead back to the simple evolutionary formula of survival, an opinion which was commonly held a generation ago, then almost disappeared from the literature, and now seems to be coming back into favor.

As everybody knows, when tuberculosis is introduced among a race to which it is new, it is many times more fatal than it is even among the most ignorant and unhygienic of "civilized" people, frequently taking an acute and general form. In explanation, the hypothesis has been advanced that these savages fail to resist because they have not had the immunizing benefit of a first infection in childhood. If this were the whole story, such acutely fatal cases of tuberculosis should be common among children of urbanized races, but actually they are rare. Again, it has been suggested that owing to our relatively good hygiene our children become infected with small numbers of bacilli, perhaps attenuated by drying and light. This is doubtless often true and important, but we have in our cities many children living in the most crowded and

unwholesome quarters swarming with tubercle bacilli from some sick and careless consumptive, and, while they become infected and many of them eventually die of tuberculosis, it is unusual to get the high percentage of acutely fatal cases seen in such material as the Senegalese troops transferred to Europe during the war.

Among races whose exposure to tuberculosis began a century or more ago we observe a pretty constant series of phenomena. At first the death-rate was tremendous. Some small isolated groups were exterminated. But whenever the group was large enough there were survivors, since all living beings exhibit a scale of variation in every function, including resistance to unfamiliar diseases. Succeeding generations showed high but diminishing death-rates, approaching but not reaching the low level of races long exposed.

It has been objected that this increase in resistance takes place too fast to be an evolutionary process. No doubt it is very largely influenced by hygienic factors and factors of morale, both so vital in any race's or individual's resistance to tuberculosis. But a factor which tends to kill off all the ill-adapted, the nonresistant, before they are old enough to reproduce, while allowing the relatively well-adapted to survive long enough to leave descendants, can make itself felt in a very few generations.

The evolutionary view seems to account satisfactorily for the high resistance of our children to first infection, assuming constant hygienic conditions. On the other hand, the effect of first infection and the primary complex upon subsequent reaction does not as yet seem susceptible of clarification by any simple concept.

I have emphasized innate immunity as being, in my opinion, apart from hygienic conditions, the most practically important advantageous factor now known to us in our conflict with tuberculosis. The changes in the behavior of our tissues which follow natural first infection, while of immense interest, seem to me, in sum, not advantageous, and probably the reverse. It has been suggested that these changes, which result in the rapid sloughing of sensitized tissues together with the living tubercle bacilli which have invaded them, are especially dangerous in the lung, with its communication-system of branching bronchi and its in-and-out current. The abortive attempt of the "immune" tissue to slough the lesion results in the aspiration of the bacilli to other points, where the same process tends to be repeated, and so on. This concept is certainly pictured in the lungs of most persons dead of phthisis.

Nobody can deny that experimental procedures of various kinds, with dead bacilli, attenuated bacilli, and very small numbers of virulent bacilli, have had some success in raising the resistance of animals to the tubercle bacillus. It is hardly probable that we are all wrong about this, and if we are right these experiments are examples of acquired immunity. It is then possible to stimulate the protective functions, and it should be possible to evolve a technique for applying the process to man. But these functions, which apparently can be stimulated, can, as Theobald Smith suggests, probably be exhausted too. Certainly the effect upon them of natural first infection in the human species does not appear to be the production of practical immunity. For it seems strange to call a quality by the name of immunity, if you get well when you do not have it and die when you have it. Sensitization seems the more appropriate term.

Because an adequate bibliography to this short paper would have to include hundreds of titles, I have purposely avoided references to authors with the exception of Dr. Smith, to whom I am indebted for an early realization of the great importance of heredity in all biological phenomena.

SUMMARY

1. The great majority of individuals have a high degree of resistance to all common infectious diseases, including tuberculosis.

2. This resistance is an innate or inherited characteristic, and it is manifest on first infection, though it is possible that it is not always fully developed at birth.

3. A race long exposed to a disease has a much higher innate resistance to it than a race newly exposed.

4. In the case of endemic diseases, or "universal viruses," to which practically all persons are exposed, first infection usually takes place in the first years of life. The great majority combat these first infections successfully, because of their innate resistance. A minority, whose resistance is naturally low, or is not yet fully developed, or is overwhelmed, succumb and are eliminated, accounting for the high death-rate in the first years of life from all these diseases. Between early childhood and adolescence the death-rates from all diseases are remarkably low, though to the best of our knowledge most first infections with endemic diseases occur in this period.

5. In the case of an endemic disease in which recovery is followed by a marked and prolonged increase in specific resistance, practically all deaths occur in infancy and childhood, the period of first infection. Such diseases become known as children's diseases. Diseases which are not followed by a marked increase of immunity, on the other hand, show high death-rates in maturity and old age.

6. In the case of tuberculosis first infection in childhood is usually very well resisted. It produces no illness as a rule, and is attended by a very low death-rate. This resistance on *first encounter* with the tubercle bacillus must be an inherited trait. After this period the death-rate rises rapidly and maintains a high level throughout the rest of life. This is in the sharpest contrast to the immunity-conferring diseases, and indicates that natural first infection with the tubercle bacillus, though well resisted, is not followed by any effective increase in immunity, but rather the reverse. Especially in pulmonary tuberculosis the altered tissue reaction following first infection seems to favor the development of disseminated ulcerative phthisis.

7. Certain forms of vaccination evidently raise the resistance of animals to the tubercle bacillus, and there may be reason to hope for something from the application of such methods to man, since they prove that acquired immunity is a potential reality. But any method, to succeed, must work better than natural first infection, which appears to sensitize more than it protects.

A STATISTICAL STUDY OF THE RELATIONSHIP BETWEEN PREGNANCY AND TUBERCULOSIS[1]

ALICE M. HILL

With an introduction by

H. R. M. LANDIS

INTRODUCTION

The importance of the subject with which this report deals cannot be overemphasized. Every year thousands of tuberculous women become pregnant, and, in addition, thousands of women of child-bearing age die of tuberculosis. It is quite apparent, therefore, that physicians are constantly confronted with the possibility of this combination.

It is well known that a tuberculous lesion may remain latent for an indefinite time, providing the natural resistance is not overtaxed. Pregnancy is one of the factors often responsible for overtaxing the resistance sufficiently to convert a latent, inactive lesion into an active one. It is surprising how many women will date the onset of their illness from a pregnancy. It is also of interest to note that one of the factors brought out in this report is that the danger is greatest in the first pregnancy. In other words, if a woman has withstood the possible danger of one or two pregnancies, the likelihood is that she possesses sufficient resistance to prevent her tuberculosis from becoming clinically active.

The problem of pregnancy and tuberculosis has two aspects: (1) that of the woman who is known to have tuberculosis, and (2) the unsuspected case in which the disease manifests itself during pregnancy or, more often, shortly after the birth of the child.

In those who are known to have tuberculosis, the problem from the physician's viewpoint offers little difficulty. A woman who has had active tuberculosis should not attempt to bear children until sufficient time has elapsed to establish a reasonable certainty that her disease is arrested. How long should this interval be? There can be no fixed rule. Each individual must be advised according to the severity of the attack, the amount of pulmonary involvement present and the length of time needed to bring about the arrest of the disease. While it must be admitted that

[1] From the Statistical Service of the National Tuberculosis Association, New York City.

the advice to defer marriage is rarely followed, it is none the less the duty of the physician to warn women of the possible consequences.

Of more importance is the group in which tuberculosis is unsuspected. It is in this group that so many tragedies occur, many of which could be avoided. It is now the universal practice to safeguard the woman against the dangers of the toxemias of pregnancy by performing, at regular intervals, urinary tests and making estimations of the blood pressure. These simple procedures have been the means of sparing thousands of women the horrors of eclampsia. In the Prenatal Clinic at the Phipps Institute, during a period of fifteen years, there has not been a case of eclampsia in a woman who had been under supervision for any reasonable length of time, and this is true in other similar clinics and is becoming more and more true in medical practice at large.

It is becoming more and more evident that a complete knowledge of the pregnant woman's condition is essential. She should be regarded as a sick woman, or perhaps it would be better to express it in this way: Facing, as she does, risks over and above those of her nonpregnant sister, every effort should be made to see that she is organically sound. It cannot be too strongly emphasized that the necessity of carefully examining the lungs is as important as similar examinations of the heart and kidneys. A complete medical history should be taken in all cases. This is the most certain means of obtaining information of importance relative to the lungs. Thus, exposure to tuberculosis in the family, a past history of haemoptysis, pleurisy, or fistula-in-ano, point strongly to the presence of a pulmonary lesion. Keeping in mind the fact that the examination of the lungs in women with such a history is often inconclusive, one should not assume that, in the event of a negative or doubtful examination, these women can be passed as normal. These danger signals are of the utmost value, and if heeded will often enable the physician to take cognizance of symptoms developing during the course of the pregnancy which he might otherwise ascribe to the pregnancy itself.

If this report accomplishes nothing more than to focus attention on the frequency with which this widely prevalent disease is associated with an equally prevalent physiological condition, it will have served a valuable purpose.

A question of great importance to the tuberculous woman, and one which the physician is frequently called upon to decide, is whether she

may become pregnant, or, if already pregnant, whether the pregnancy may be allowed to proceed to term.

Many years ago the belief was widespread that pregnancy improved the tuberculous woman's condition. In some lay quarters, at least, this belief still prevails. Later that school gained the ascendency whose tenet was that the effect of pregnancy upon the course of tuberculous disease was in every instance baneful.

The relationship between pregnancy and tuberculosis has been much discussed in recent years. The *International Union Against Tuberculosis* devoted one day of the meeting at Lausanne in 1924 to the subject. Tuberculosis specialists have been interested, but probably the majority of the discussions in this country and others have emanated from obstetricians. Even the important report which Dr. Forssner of Stockholm presented at Lausanne was based upon women confined in two maternity hospitals in Stockholm, supervised subsequently by tuberculosis dispensaries, although the control group of women whose tuberculosis was not complicated by pregnancy was exclusively of dispensary patients.

The National Tuberculosis Association has hoped to contribute some additional data by approaching the problem from a somewhat different direction. Instead of women, by chance tuberculous, known to obstetricians, the women studied have been known to tuberculosis specialists with pregnancy an incident in their history.

This study, made purely from records, is based primarily upon white tuberculous women known to the tuberculosis clinics of Detroit, Michigan. Detroit was selected because the tuberculosis-clinic work of the city is handled entirely by the Department of Health and, therefore, more histories were assumed to be available through this one source than were likely to be elsewhere, except in cities considered too large for this study. Every record in the clinic files was inspected, but only those of tuberculous women known to the clinic at some time during the period January 1, 1920, to December 31, 1924, were included in the study. Histories were drawn from the records of tuberculous women who had had pregnancies which had terminated during the period mentioned and which accompanied or immediately preceded the tuberculous disease, whether the pregnancy resulted in a live child born at term, a stillbirth, a premature live birth, or an abortion, therapeutic or otherwise. Histories were also obtained of married tuberculous women of childbearing age who had not been pregnant for at least a year prior to their diagnosis and whose pregnancies, if any, did not immediately precede the disease.

The histories of these nonpregnant women were taken for purposes of comparison with those of the pregnant women. Those women only were considered who had been known for at least a year or who had died within the twelvemonth.

Many of the clinic patients whose records were transcribed were known to various other agencies and institutions. In order that the fullest possible history of those studied might be obtained, so far as possible the records for each were examined in each agency to which they were known. Thus aside from those in the tuberculosis clinics, records were read in the municipal sanatoria, Herman Kiefer Hospital and Spring Hills Sanatorium, in the Detroit Tuberculosis Sanatorium, a private institution, and in approximately twenty-five other hospitals and medical and social agencies. The National Tuberculosis Association is most appreciative of the considerable assistance given by these organizations, and especially of that by the Health Department of the City of Detroit without whose coöperation the study could not have been undertaken in that city.

Each woman included in the study had been definitely diagnosed as tuberculous by a physician.

This study includes 349 women whose pregnancies occurred during or immediately preceding pulmonary tuberculous disease, and 160 women who had never been pregnant or whose pregnancies were in no sense associated with tuberculosis, and who serve as a control group. This control group represents 46 per cent of the number of women in the pregnant group. While it would be highly desirable to have a larger number of controls it seems that the findings as to the effect of the disease on the two groups are significant because of the comparability of the groups.

The aim was to obtain for each pregnant woman a control who would be not only in the same stage of the disease but who would be of approximately the same age, as well as of the same nationality, with the same history as to presence or absence of tubercle bacilli in the sputum, and with about the same amount of sanatorium care. Histories were transcribed of the great majority of women known to the tuberculosis clinic for a sufficient length of time whose tuberculosis was unassociated with a pregnancy. Had the stage of the tuberculous disease been the single factor to be taken into consideration it would have been a simple matter to obtain the desired number of cases comparable with those of the pregnant women. But it is evident that a patient thirty-eight

years of age is not properly comparable with a patient seventeen years of age, even though both may be in the minimal stage of tuberculosis. Neither is a Russian Jew comparable with an Irish woman. Since age and nationality are held to influence the course of tuberculosis in a patient they must be taken into consideration in choosing a control group. So also should be the other items mentioned. The first obstacle to obtaining the desired number of histories for comparative purposes was age. The married tuberculous women under twenty years of age, who were pregnant while tuberculous or immediately before, far outnumbered the married tuberculous women of the same age whose disease did not exist about the time of a pregnancy. This may have no significance so far as the incidence of tuberculosis is concerned; it may and probably does mean merely that the great majority of married women under twenty have a history of pregnancy, but the fact remains that only a small number of controls could be found for those in this age-group. And, as might have been expected, in the later child-bearing years the situation was reversed. Even when patients in the one group were found comparable with patients in the other as to age and stage of the disease it was not always possible to find a pair of the same nationality. Table 1 shows the measure of comparability of the two groups. It calls for no further discussion.

The report throughout concerns itself with the condition of the patient one year after the end of the pregnancy, except where specifically noted otherwise, as the situation at this time presents the clearest picture. The large number of patients at subsequent intervals whose condition is unknown make the figures for those of specific known condition of little or no value. It is evident that many of the patients could not have been known for much more than a year after their labor, since the clinic and other records were examined about one year after the close of 1924; and, of course, a number passed out of the picture for other reasons. In this analysis the status of the patient has been designated as "Dead," "Worse," "Unchanged," "Improved," "Living, otherwise unknown," or "Unknown." This terminology is not satisfactory but is possibly the best that could be devised with the data available for making the decision as to the condition of the patient. It was in the nature of things impossible to obtain records on each and every case which would state with scientific precision the degree of severity of the symptoms correlated with the extent of lung involvement at specified intervals before, during and after the pregnancy.

TABLE 1A

Nativity and parentage of tuberculous pregnant women and of tuberculous controls

TIME OF DIAGNOSIS AND STAGE OF DISEASE*	TOTAL		NATIVE-BORN BY COUNTRY OF BIRTH OF PARENTS																FOREIGN-BORN, BY COUNTRY OF BIRTH																						UNSPECIFIED OR UNKNOWN PARENTAGE	
			Total native-born		United States		Poland		Germany		Canada		Mixed United States and foreign		Other foreign		Unspecified or unknown		Total foreign-born		Poland		Russia		Italy		Austria		Canada		Hungary		Rumania		England		Greece		Syria, Armenia, Turkey		Other foreign			
	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls
Total	160	160	92	93	54	58	4	2	8	15	4	3	8	3	6	10	8	2	67	67	25	24	8	8	5	5	7	5	5	6	5	6	4	1	4	4	1		1	3	7	1	
Before pregnancy	56	56	31	30	11	13	2		4	7	3	2	3	2	3	5	5	1	25	26	7	8	6	2	3	4	2	1	1	1	1	1	1							1	4		
Minimal	32	32	21	20	7	9	1		3	5	2	1	3		1	4	4	1	11	12	1	2	6	4	1	1	2		1	1				1							3		
Moderately advanced	22	22	10	10	4	4	1		1	2	1	1		2	2	1	1		12	12	6	6	2	2		1	1	1			1	1	1							1	1		
Far advanced	2	2																	2	2					1	1	1	1															
During pregnancy	36	36	17	18	12	13	1	1		2			2		1	1	1	1	19	18	6	6		1	2	1	1	1	2	2	2	2		3	3	1			1	1	1		
Minimal	17	17	10	10	6	7	1	1		2			2		1				7	7	2	1			1	1	1	1		1		1		2	2					1			
Moderately advanced	16	16	6	7	5	5										1	1	1	10	9	4	4		1	1				1	1	1	1	2		1	1				1		
Far advanced	3	3	1	1	1	1													2	2		1									1				1						1		
After pregnancy	68	68	44	45	31	32	1	1	4	6	1	1	3	1	2	4	2		23	23	12	10		1	1	1	2	2	3	3	2	3	1		1	1				1	2	1	
Minimal	16	16	12	13	10	11			1	1		1			1				3	3	1	1					1	1			1	1										1	
Moderately advanced	33	33	21	21	12	12	1	1	3	4	1		2	1	1	3	1		12	12	7	6			1	1			2	2		1			1	1				1	1		
Far advanced	19	19	11	11	9	9				1			1			1	1		8	8	4	3		1			1	1	1	1	1	1			1	1					1		

*"Time of diagnosis" applies only to pregnant women, not to controls; "stage of disease," to both.

The primary question to which this study attempted to find an answer was, "What effect does pregnancy have upon the course of pulmonary tuberculosis?" More data are necessary for a final answer. The findings of this study may be only indicative. But a comparison of the figures for 160 of the women whose pregnancies accompanied or imme-

TABLE 1B

Age of tuberculous pregnant women and of tuberculous controls

TIME OF DIAGNOSIS AND STAGE OF DISEASE*	TOTAL		UNDER 20		20–24		25–29		30–34		35–39		40–44		45 AND OVER	
	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls
Total	160	160	2	1	46	43	45	43	41	43	22	23	3	6	1	1
Before pregnancy	56	56	1		13	8	15	13	16	20	11	12		3		
Minimal	32	32			10a	5	7b	9	8b	9	7b	8		1		
Moderately advanced	22	22	1c		3b	3	8d	4	8b	11	2c	3		1		
Far advanced	2	2									2	1		1		
During pregnancy	36	36	1		11	12	9	9	9	7	6	8				
Minimal	17	17	1		6	7	3	3	4	3c	3	4				
Moderately advanced	16	16			4	4	5	5	4	3c	3	4				
Far advanced	3	3			1	1	1	1	1	1						
After pregnancy	68	68		1	22	23	21	21	16	16	5	3	3	3	1	1
Minimal	16	16		1	5e	5	4e	3	5	6	2e	1				
Moderately advanced	33	33			9	9	11	11	7e	8	2e	1	3	3	1	1
Far advanced	19	19			8	9	6e	7	4f	2	1	1				

*"Time of diagnosis" applies only to pregnant women, not to controls; "stage of disease," to both.

a. Six mothers were in later age-period when pregnancy terminated.
b. Two mothers were in later age-period when pregnancy terminated.
c. One mother was in later age-period when pregnancy terminated.
d. Five mothers were in later age-period when pregnancy terminated.
e. One mother was in later age-period when pregnancy terminated.
f. Two mothers were in later age-period when pregnancy terminated.

diately preceded their tuberculosis with those for their controls regarding their condition at one year and at two years after diagnosis (and in the case of the pregnant women, after conception or confinement) leads to the conclusion that pregnancy apparently had no appreciable bearing upon the progress of the tuberculous disease. (See table 2.)

The women who had pregnancies associated with tuberculosis fall at once into three groups: those diagnosed before conception occurred, those diagnosed during pregnancy, and those diagnosed after labor. In connection with the first of the three groups it should be noted that the pregnancy considered in this study, with its concomitant conditions, has been the first terminated in the 1920–1924 period. In a few instances one or more previous gestations have occurred since the diagnosis of tuberculosis; these are discussed later in the report.

TABLE 1C

Sputum findings of tuberculous pregnant women and of tuberculous controls

TIME OF DIAGNOSIS AND STAGE OF DISEASE*	TOTAL		POSITIVE		NEGATIVE		UNKNOWN	
	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls	Pregnant women	Controls
Total	160	160	64	74	60	66	36	20
Before pregnancy	56	56	12	26	31	26	13	4
Minimal	32	32	4	10	19	19	9	3
Moderately advanced	22	22	7	14	11	7	4	1
Far advanced	2	2	1	2	1			
During pregnancy	36	36	12	18	18	18	6	
Minimal	17	17	1	4	15	13	1	
Moderately advanced	16	16	8	11	3	5	5	
Far advanced	3	3	3	3				
After pregnancy	68	68	40	30	11	22	17	16
Minimal	16	16	4	1	5	14	7	1
Moderately advanced	33	33	23	15	4	8	6	10
Far advanced	19	19	13	14	2		4	5

* "Time of diagnosis" applies only to pregnant women, not to controls; "stage of disease," to both.

Between the women diagnosed after confinement—minimal, moderately advanced, and far advanced—matched to controls and the latter the differences at one and two years after diagnosis were negligible. Of the women diagnosed during their pregnancy more were dead one year after diagnosis than in the group of nonpregnant women otherwise comparable with them; at the end of two years, however, the difference in the condition of the two groups was slight. It may be that in a considerable number of instances the tuberculosis of those not diagnosed until during or after pregnancy was advanced by the pregnancy, but

TABLE 2

A comparison of the condition at one year and at two years after diagnosis of tuberculous pregnant women according to when diagnosed and of tuberculous controls

STAGE OF DISEASE AT DIAGNOSIS WITH CONDITION AT ONE YEAR AND AT TWO YEARS LATER	TUBERCULOUS WOMEN							
	Total		Group I: Diagnosed before pregnancy	Group Ia: Controls to Group I	Group II: Diagnosed during pregnancy	Group IIa: Controls to Group II	Group III: Diagnosed after pregnancy	Group IIIa: Controls to Group III
	Pregnant women	Controls						
One year after diagnosis	160	160	56	56	36	36	68	68
Minimal	65	65	32a	32	17	17	16g	16
Dead	2	3		3	1		1	
Living	54	62	32	29	12	17	10	16
Unknown	9				4		5	
Moderately advanced	71	71	22c	22	16	16	33h	33
Dead	26	27	2	5	6	2	18	20
Living	36	44	20	17	5	14	11	13
Unknown	9				5		4	
Far advanced	24	24	2	2	3	3	19i	19
Dead	17	17	1e	2	2	1	14f	14
Living	6	7	1			2	5	5
Unknown	1				1			
Two years after diagnosis	160	160	56	56	36	36	68	68
Minimal	65	65	32b	32	17	17	16	16
Dead	3	4		4	1		2	
Living	45	47	31	26	9	10	5	11
Unknown	17	14	1	2	7	7	9	5
Moderately advanced	71	71	22d	22	16	16	33	33
Dead	32	36	4	9	7	5	21	22
Living	26	28	17	11	3	8	6	9
Unknown	13	7	1	2	6	3	6	2
Far advanced	24	24	2	2	3	3	19	19
Dead	21	21	2e	2	2	2	17f	17
Living	1	1				1	1	1
Unknown	2	2			1		1	1

a. One year after conception 29 were living, 3 unknown.
b. Two years after conception 21 were living, 11 unknown.
c. One year after conception 3 were dead, 19 living.
d. Two years after conception 5 were dead, 14 living, 3 unknown.
e. One died of diphtheria.
f. One died of endocarditis.
g. One year after delivery 11 were living, 5 unknown.
h. One year after delivery 11 were dead, 20 living, 2 unknown.
i. One year after delivery 12 were dead, 7 living.

the figures for the women diagnosed before pregnancy would indicate that it need not have been if the woman's tuberculous condition had been recognized sufficiently early and she placed under appropriate care. Between the women diagnosed before pregnancy and their controls the differences were more noticeable than in either of the other groups, and it was in favor of the pregnant woman. The mortality was greater among the controls than among the pregnant women in each stage of the disease, both at one year and at two years after diagnosis, and also after conception in the case of the latter. These data of course should not be construed to mean that pregnancy should be advocated for the tuberculous woman, but they would seem to indicate that the pregnant tuberculous woman, under treatment for tuberculosis, faces a risk no greater than that of the tuberculous woman plus that of the normal woman who becomes pregnant.

However, the time with respect to the pregnancy at which the patient was diagnosed as having tuberculosis seemed to have a most important bearing upon the results. The earlier the diagnosis, the less the danger to the mother. Less than one in twelve of the women diagnosed before pregnancy was dead a year after its close, one in five of the women diagnosed during pregnancy was dead and one in three of those diagnosed after confinement.

The stage the tuberculous disease had attained in these mothers revealed a similar close relationship to the time with respect to the pregnancy at which the diagnosis was made. Of the women diagnosed before they became pregnant only six were far advanced, active, and one far advanced, inactive. Eight of those diagnosed during their pregnancy were far advanced. But of those diagnosed subsequent to delivery 44, or about one-third, were far advanced.

It might be said that such a large proportion of the mothers diagnosed after confinement, as compared with those diagnosed before and during pregnancy, died because so many of them were far-advanced cases, but the truth probably is that their mortality was so great because their illness was permitted to progress to such an advanced stage before it was diagnosed. For instance, the one woman in this group who died within six weeks of her delivery of a full-term child was far advanced at diagnosis although the onset of her illness was placed as before pregnancy.

Inasmuch as pregnancy brings more or less physical stress to the normal woman, it is to be expected that it would do the same for the tuberculous woman. But from the fashion in which those diagnosed before

pregnancy survive the experience, it is reasonably clear that the woman who knows she is tuberculous and who follows out the regimen for the usual tuberculosis patient similar to herself will pass through the gravid state with results approximately what they would have been had she not been pregnant. These data would seem to point, not to any action dealing with the condition of pregnancy *per se*, but rather to the need for early diagnosis of the patient's condition followed by appropriate treatment of her tuberculosis. It is quite safe to say that had each of these women been given a *thorough* chest examination at the time her gravid

TABLE 3

Condition one year after delivery of women diagnosed before pregnancy

STAGE OF DISEASE BEFORE PREGNANCY	CONDITION OF WOMAN ONE YEAR AFTER DELIVERY						
	Total	Dead	Worse	Unchanged	Improved	Living, otherwise unknown	Unknown
Total	136	11	18	42	31	9	25
Minimal	67	1	6	23	19	6	12
Minimal, inactive	18	1	2	9	1	1	4
Moderately advanced	35	6	7	7	8	1	6
Moderately advanced, inactive	4		1	1	1		1
Far advanced	6	3	1	1	1		
Far advanced, inactive	1			1			
Unspecified	4		1		1	1	1
Unspecified, inactive	1						1

condition was discovered, the mortality of those not diagnosed until during their pregnancy or subsequent to confinement would have been much less.

EFFECT OF PREGNANCY UPON THOSE DIAGNOSED PRIOR TO IMPREGNATION

One year after their pregnancies had terminated 11 of the 136 women who had been diagnosed prior to impregnation were dead, 18 were classed as worse, 42 as unchanged, and 31 as improved; 9 were living but their condition was otherwise unknown, and the status of 25 was entirely unknown. (See table 3.)

A study of the deaths discloses that the blame for them does not rest entirely upon the tuberculous disease. One patient, a minimal case at diagnosis, died of influenza during a confinement at seven months. One,

incipient, apparently arrested at diagnosis, died a few hours after a Caesarean section, her tuberculosis remaining inactive according to the attending physician. One, far advanced, died of diphtheria ten days after the birth of a child stillborn at seven or eight months of gestation.

Of the remaining eight patients in this group who were dead one year after the cessation of the pregnant state six were moderately advanced and two far advanced prior to the pregnancy. One of the former died during a pregnancy of which almost nothing is known; three died in less than six weeks after childbirth, all having failed during pregnancy (one

TABLE 4

Condition one year after delivery of women diagnosed during pregnancy

STAGE WHEN DIAGNOSED, WITH TIME OF ONSET	CONDITION OF WOMAN ONE YEAR AFTER DELIVERY						
	Total	Dead	Worse	Unchanged	Improved	Living, otherwise unknown	Unknown
Total	65	13	11	5	2	19	15
Onset before pregnancy							
Minimal	18			2		11	5
Moderately advanced	18	5	2	2		6	3
Moderately advanced, healed	1			1			
Far advanced	7	2	2		1	1	1
Unspecified	1				1		
Onset during pregnancy							
Minimal	7	2	3				2
Moderately advanced	7	2	2				3
Far advanced	1	1					
Onset uncertain							
Minimal	1		1				
Minimal, inactive	1					1	
Moderately advanced	3	1	1				1

had advanced from minimal to moderately advanced during the five months before her pregnancy; one of the births was premature); one had become a far-advanced and intestinal case during a brief two months' pregnancy terminated by a therapeutic abortion after which she lived less than two months; another died about eleven months after labor at full term. Of the two who were far advanced prior to impregnation one died the day she was delivered of a seven months' child and the other about five months after her delivery at full term.

EFFECT OF PREGNANCY UPON THOSE DIAGNOSED DURING ITS COURSE

Of the 65 women who were diagnosed during their pregnancy, a smaller proportion were living one year after its termination than among those diagnosed before pregnancy. Thirteen, or exactly one-fifth of this second group, were dead at the end of the year, 11 were worse, 5 unchanged, 2 improved, 19 living but condition otherwise unknown, and the status of 15 was unknown. (See table 4.)

This group diagnosed during the period of gestation divides into those cases in which the first symptoms of tuberculosis appeared before pregnancy, 45, those in which the onset occurred during pregnancy, 15, and 5 others for whom information as to the time of onset with reference to the pregnancy was not available.

Among the 13 who were dead in less than a year after the close of their pregnancies, 7 showed symptoms of the disease before and 5 during pregnancy, and for 1 this point was not known. Five of the deceased patients who were ill prior to gestation were moderately advanced and two were far advanced before it was recognized that they were suffering from tuberculosis. Of the former one died when six months pregnant, three within six weeks of delivery (one after an eight months' pregnancy) and one about eleven months after confinement. The two patients far advanced at diagnosis passed away in less than a month after their delivery (the pregnancy of one was of only eight months' duration). The five dead whose illness had its onset during pregnancy included two who were minimal cases at diagnosis, of whom one died within six weeks of delivery and the other about eight months afterward. (The latter, an unmarried mother, placed the onset as coincident with conception.) They also included two women, moderately advanced at diagnosis, of whom one died of smallpox when five months advanced in gestation and the other four months after delivery; and one far-advanced patient who died eleven days after delivery. The patient for whom the period of the onset of the disease was uncertain died ten weeks after a Caesarean section at eight months.

EFFECT OF PREGNANCY UPON THOSE DIAGNOSED SUBSEQUENT TO CONFINEMENT

The greatest mortality was found among the women who were diagnosed after the termination of their pregnancies. Of the 148 in this group 47 were dead one year after delivery, 78 were reported as worse

than before pregnancy, 1 improved, 9 living but with condition otherwise unknown, and 13 as entirely unknown. (See table 5.) Of course some improved subsequent to diagnosis, but their number was small and the improvement seldom of long duration. The truth of this is indicated by the figures for deaths in subsequent years among those diagnosed after

TABLE 5

Condition one year after delivery of women diagnosed after pregnancy

STAGE WHEN DIAGNOSED, WITH TIME OF ONSET	CONDITION OF WOMAN ONE YEAR AFTER DELIVERY						
	Total	Dead	Worse	Unchanged	Improved	Living, otherwise unknown	Unknown
Total	148	47	78		1	9	13
Onset before pregnancy							
Minimal	11		2		1	7	1
Moderately advanced	16	6	8			2	
Far advanced	12	9	3				
Onset during pregnancy							
Minimal	7	1	5				1
Moderately advanced	15	5	8				2
Far advanced	7	5	2				
Unspecified	1						1
Onset after pregnancy							
Minimal	17		11				6
Moderately advanced	33	5	27				1
Far advanced	23	13	9				1
Unspecified	3	1	2				
Onset uncertain							
Moderately advanced	1		1				
Far advanced	2	2					

delivery. As has been stated above, 47 were dead one year after the termination of the pregnancy. At the end of two years, 75 were known to be dead; at the end of three years, 85; at the end of four years, 90; and at the end of five years, 92. Nothing is known regarding any of the others at the end of five years, with three exceptions, in a number of instances because five years had not yet elapsed since the birth. It is highly probable that the actual number of these women who were or would be dead at the end of five years was greater than the records

reported as dead. In any event, the relative number of known dead in this group was much greater than among those diagnosed before and during pregnancy. At the end of five years, of the group diagnosed before impregnation only 24 were known to be dead with 106 unknown; and among those diagnosed while in a gravid condition 17 were known to be dead as compared with 47 unknown. While it is well recognized that the real situation at the end of five years cannot be arrived at from any such figures, no reason is apparent why the proportion of known deaths should be so much greater or less in one group than in another except that the actual number of deaths was larger or smaller.

The first symptoms of tuberculous disease in the mothers who were not diagnosed until after the conclusion of their pregnancies appeared with 39 before conception, with 30 during pregnancy, and with 76 after confinement, and for three this was not known.

PREGNANCIES OF LESS THAN FULL TERM

Interest is frequently expressed in the result of the premature termination of pregnancy in a tuberculous woman, especially if the termination has been induced. The number of pregnancies of less than full term which came to light during the study is so small that the discussion of them here will be of no real value but may be of some interest. Disregarding the three instances in which the foetus died *in utero* with the mother, there were 41 pregnancies which came to an end spontaneously prior to term, 11 which were terminated by a physician, and one in which the miscarriage was self-induced. In at least 17 cases the issue was seven months or more advanced, and in two others was stated to be "Premature."

One woman, a minimal case, of those whose pregnancies were terminated by a physician was reported to be improved one year later. Five others were worse. It is interesting to note that three of these five were aborted before they were diagnosed as tuberculous. Two women aborted for therapeutic reasons died within the year. The condition of two was reported as unchanged. The other patient was reported still living but her exact state of health was not known.

The woman whose abortion was self-induced was working and feeling much stronger six months later, though not gaining in weight.

Of those pregnancies terminated spontaneously prior to term 20 were in women diagnosed prior to the period of gestation, 7 in those diagnosed

during pregnancy, and 14 in those diagnosed subsequent to the abortion. Among the group diagnosed before the pregnancy five women were reported improved, six unchanged, four worse, one unknown, and four dead. These dead included a patient who died in confinement of influenza and one who died of diphtheria ten days after delivery. The spontaneous deliveries of the women diagnosed during pregnancy occurred for the most part in the later months. One year after confinement two were dead, one worse, two living but otherwise unknown, and two were unknown. Of those women diagnosed after confinement those diagnosed as minimal, six in number, had all miscarried in the earlier months. Those diagnosed in later stages had miscarried in the later months of pregnancy in six of the eight instances; in two, this point was not known. It should be observed that two of the minimal cases diagnosed after confinement and one of the moderately advanced were recorded as having a specific disease. None of the patients diagnosed before or during pregnancy, whose deliveries prior to term were spontaneous, was so recorded. At the end of the year one woman spontaneously aborted was known to be dead, nine were worse (and one of these may have been dead), one was reported improved, two were living but otherwise unknown, and two were unknown.

PREVIOUS PREGNANCIES OF THESE MOTHERS, TERMINATED SINCE ONSET AND DIAGNOSIS

More pregnancies related to their disease appeared in the histories of the tuberculous mothers than just those about which the study has centered. Seventy-five women reported pregnancies preceding that of the study but terminating following the appearance of symptoms of their illness. Their number included 56 women diagnosed before, 10 during and 9 after the pregnancy of the study. However, only 23 reported deliveries between diagnosis and the pregnancy considered.

Among the women diagnosed *prior* to the pregnancy of the study was one reported to have had five pregnancies terminating, one and possibly two of them in abortions, in the course of eight years after the onset and diagnosis of her tuberculosis but before the birth of this child. This patient's disease never progressed beyond the minimal stage, and one year after the birth of the child included in the study she was improved and classed as quiescent. Seven women reported themselves pregnant three times between the onset and this pregnancy. Of their number only one, a patient whose first symptoms appeared nearly twelve years

before and who was diagnosed five years before and bore a child about the time of diagnosis, died within the year, and she died of diphtheria shortly after the delivery of a premature stillborn child. Another, moderately advanced, thrice pregnant between the onset and diagnosis and this pregnancy, was unchanged. Another moderately advanced patient pregnant three times since onset and diagnosis thirteen years before was worse. One minimal and one moderately advanced, inactive, were unchanged; the status of one, moderately advanced, was unknown; and one, of unspecified stage, was living but otherwise unknown. In the case of each of the last four no pregnancy had occurred between the diagnosis and the pregnancy of the study. Two of the three pregnancies of the patient diagnosed as minimal were miscarriages.

The number of women diagnosed before the present pregnancy who had been confined twice since the onset of their tuberculosis was fifteen. Three of the number had been confined twice since diagnosis as well as onset, one minimal, one moderately advanced, inactive, and one of unspecified stage, all of whom were improved a year after the confinement of the study. Four had been pregnant once between onset and diagnosis and once between diagnosis and the child of the study; they embraced one minimal and one moderately advanced patient who improved, one minimal who remained unchanged and another who was unknown at the end of the year. The eight who had been twice pregnant since the onset but not at all since diagnosis comprised one minimal and one moderately advanced case who were improved, two minimal, two minimal, inactive, and one far advanced, who were unchanged, and one minimal who was living but otherwise unknown.

The number of women in the group diagnosed before pregnancy who were confined once between the onset of their illness and the pregnancy of the study was 33. Eleven or twelve of them were not diagnosed until after the birth of the preceding child. Their status a year after the termination of the pregnancy of the study was, according to the stage of their tuberculosis before it, as follows:

Dead

1 moderately advanced
1 minimal (onset during the previous pregnancy)

Worse

2 minimal*
1 minimal, inactive
2 moderately advanced**
1 moderately advanced, inactive†
1 stage unspecified†

Unchanged

8 minimal§
2 minimal, inactive**
1 moderately advanced
1 far advanced, inactive†

Improved

2 minimal**
1 minimal, inactive†
3 moderately advanced
1 far advanced

Unknown

3 minimal**
1 moderately advanced
1 stage unspecified, inactive

* One, possibly the other, not diagnosed until after previous pregnancy.
** One not diagnosed until after previous pregnancy.
† Not diagnosed until after previous pregnancy.
§ Two not diagnosed until after previous pregnancy.

Among the women who were not diagnosed as tuberculous until *during* this pregnancy were ten in whom the symptoms of tuberculosis had put in an appearance long enough before for them to have been pregnant meantime. A patient who had been thus pregnant four times, a minimal case, was unchanged a year after the birth of this child. One, moderately advanced, who had been three times pregnant since the onset, was worse. Of three patients, all minimal cases, twice pregnant since the onset, two were living but otherwise unknown a year after this pregnancy and the status of one was unknown. Five of these women reported one pregnancy since the onset. One of them, far advanced, was worse, and of the others, all moderately advanced, one was dead and three were living but otherwise of unknown state of health at the end of the year.

Those women who were not diagnosed until *after* the confinement of the study, although their illness was reported of such duration that they had been pregnant more than this once since it began, did not fare so well as those diagnosed before this pregnancy or during it. Of the nine three were dead at the end of the year, three were worse, and one each was improved, living otherwise unknown, and unknown.

PREGNANCIES SUBSEQUENT TO THAT OF THE STUDY

Fifty-four, or 15 per cent, of all the tuberculous pregnant women of this study were known to have been pregnant subsequent to the pregnancy upon which the study primarily has been based. Of these women

30 were found in the group who had been diagnosed tuberculous before, 12 among those diagnosed during, and 12 among those diagnosed after the pregnancy of the study.

In the group of women diagnosed *before* the pregnancy of the study who became pregnant again 19 were reported subsequently pregnant once, 7 twice, 3 three times, and 1 four times. This last patient, pregnant once between the onset and the study child, her third, diagnosed before the latter as a minimal case, was living nearly six years after the birth of the study child. Of the women three times pregnant since the study pregnancy, all minimal cases at diagnosis, one died at the birth of her last child after ten pregnancies, one multiple, in fourteen years; and two were improved about five years later when last known, the one just before the birth of the third child. Examination of the records of those women diagnosed before the pregnancy of the study who were twice pregnant after it further evidences the fact that pregnancies in tuberculous women are not necessarily dangerous providing the patient is properly instructed in how to care for herself. The condition of three was unchanged when last known, of three was improved (two markedly), and of one was somewhat worse. Among the nineteen women reported to have had one pregnancy after that about which this piece of research centres were 5 moderately advanced, 10 minimal, and 4 minimal, inactive, cases diagnosed previous to the pregnancy of the study. Every one was living at the time of the last entry on her record. The subsequent pregnancies of four women, all diagnosed as minimal, resulted in miscarriages. Nothing in the records of these cases indicated that the patients had been injured by these later pregnancies.

The data for those women diagnosed *during* the pregnancy of the study, three as moderately advanced and five as minimal cases, who were pregnant once again and for the three diagnosed as minimal and the one as minimal, inactive, who were twice pregnant subsequently, are insufficient to justify comment, though all the women were living when last known.

Neither can any lesson be drawn from the histories of the women diagnosed *after* the pregnancy of the study, 7 as minimal and 5 as moderately advanced cases of tuberculosis, who were subsequently pregnant one or more times.

ORDER OF BIRTH

In a discussion of the pregnancies of these tuberculous women two points should be made clear. The discussion is one of pregnancies,

irrespective of the length of foetal life, not of children. It is the latter for which data are given in various State and Federal reports. And the figures for the tuberculous mothers cannot be considered absolutely accurate because of the incompleteness of the records in respect to this point. However, though the actual number of pregnancies is doubtful, it is reasonably certain that it is no less than the number recorded. The figures may be considered at least indicative of the true situation.

In order to obtain some idea of how closely the order of the pregnancies of the women under consideration approximated the order of those of women in the general population, the pregnancies of the tuberculous mothers have been compared for order with the children born to white Michigan mothers during the period 1920–1924,[2] the period covered by the study. Exactly the same per cent in each group were third, fifth, seventh, eighth, ninth children and tenth or over. Twenty-nine per cent of the children in Michigan were first-born as compared with 23 per cent of the offspring of the tuberculous; and 22 per cent of the former were second children while among the latter 21 per cent were. Eleven per cent of the Michigan children were the fourth, and five per cent were the sixth, whereas twelve per cent and nine per cent, respectively, of the pregnancies of the tuberculous were.

An examination of the pregnancies of the tuberculous mothers according to when the latter were diagnosed again reveals striking differences. Fifteen per cent of the offspring of the women in the group diagnosed before pregnancy were the first, 21 per cent of those diagnosed during pregnancy, and 32 per cent of those diagnosed after confinement. Second pregnancies constituted 18 per cent of those of the women diagnosed before, 17 per cent of those diagnosed during, and 24 per cent of those diagnosed after the pregnancy of the study. Third pregnancies comprised 13 per cent, 14 per cent, and 17 per cent of the pregnancies of those diagnosed, respectively, before, during, and after gestation. Thus approximately three-fourths of the women diagnosed after confinement were diagnosed after their first, second, or third pregnancy while slightly less than one-half of the women diagnosed before pregnancy were diagnosed before such, and slightly more than one-half of those diagnosed during pregnancy were diagnosed during such.

According to the records of this study the tuberculous woman who is pregnant for the first time is the one in greatest danger. Of the eleven

[2] *Birth, Stillbirth, and Infant Mortality Statistics*, 1920, 1921, 1922, 1923, 1924, U. S. Bureau of the Census.

women diagnosed before conception who died one did so during and four after the termination of the first pregnancy. Of the thirteen women diagnosed during pregnancy who expired, four did so during or after the first pregnancy. And of 47 diagnosed after confinement who died 19, or 40 per cent, died after their first pregnancy. Of the nineteen deceased primiparae who were first diagnosed after pregnancy only one was a minimal case at diagnosis; six were moderately advanced, eleven were far advanced, and one was of unspecified stage. Of the four deceased primiparae whose diagnosis occurred during pregnancy one was a minimal case, two moderately advanced, and one far advanced when diagnosed. For the women diagnosed before pregnancy who died none other than the first appeared to have any special significance, and the significance of primiparity in this group was lessened somewhat by the fact that one of those who died was a minimal, inactive, case who died after a Caesarean section and another a moderately advanced who died after a therapeutic abortion; and that only one other primipara, a far-advanced case, was made worse, while seven remained unchanged, two were improved, and the condition of five was unknown.

The situation among tuberculous women so far as the dangers of primiparity are concerned is similar to that among women in the general population. "The most comprehensive study of the influence of order of birth upon the maternal mortality rate," says Robert Morse Woodbury in his recent *Maternal Mortality*,[3] "is that made by T. A. Coghlan[4] of data for New South Wales. He shows that for married mothers 'the risk attending the first birth is greater than at any subsequent one up to but not including the ninth.' The smallest risk was found in the second confinement, though that in the third was not much greater. After the third confinement the risk increased rapidly." The maternal mortality rate for the first child was found by Mr. Coghlan to be twice the maternal mortality rate for the second child. Among the tuberculous mothers next to the primiparae the greatest mortality occurred among the multiparae of eight pregnancies, but these women eight times pregnant were too few in number for any stress to be laid upon their mortality rate.

AGE OF MOTHER

The ages at the close of their pregnancies of those in the group of the tuberculous mothers do not differ materially from the ages of all white

[3] Woodbury, Robert Morse: *Maternal mortality*, U. S. Children's Bureau, 1926.
[4] Coghlan, T. A.: *Childbirth in New South Wales; a study in statistics*, Sydney, 1900.

mothers in Michigan at the birth of their children. The per cent distribution in the different groups for the tuberculous mothers in the study years and for the white Michigan mothers in the period 1920–1924 is given in table 6. While for the group as a whole the correspondence with the figures for Michigan is exceedingly close, when the ages of the women are considered in relation to the time when they were diagnosed the story is different. In general the ages of the patients diagnosed during pregnancy corresponded with the ages of the whole tuberculous group. But this was not the case among the women diagnosed before

TABLE 6

Per cent distribution of the tuberculous mothers of the study, and of white mothers in Michigan, 1920–1924, in each age-group

AGE-GROUP	PER CENT DISTRIBUTION				
	White Michigan mothers	Tuberculous mothers			
		Total	Diagnosed before pregnancy	Diagnosed during pregnancy	Diagnosed after pregnancy
All ages	100	100	100	100	100
10–14 years	*				
15–19 years	9	9	4	9	13
20–24 years	28	29	16	29	42
25–29 years	28	24	27	22	23
30–34 years	19	23	33	23	14
35–39 years	12	11	16	14	5
40–44 years	4	3	4	1.5	2
45 years and over	*	*		1.5	*
Unknown	*	*			*

* Less than 1 per cent.

and diagnosed after pregnancy, the ages in these two groups being the antithesis of each other. The young mothers were not diagnosed early enough with respect to pregnancy. Thirteen per cent of the mothers diagnosed after confinement were under twenty years of age when their pregnancy terminated as compared with only four per cent of those diagnosed before the pregnancy of the study. Forty-two per cent of the women diagnosed after pregnancy were from twenty to twenty-four years of age whereas only sixteen per cent were of those diagnosed before. On the other hand 33 per cent of those diagnosed before pregnancy were from thirty to thirty-four years old and sixteen per cent from thirty-five to thirty-nine; while among those diagnosed after confinement the per

cents found in these age groups were 14 and 5, respectively. Thus of those mothers who were found to be tuberculous before conception only 20 per cent were under twenty-five years of age, 47 per cent under thirty years; but of the mothers diagnosed tuberculous after confinement 55 per cent were less than twenty-five years old, 78 per cent less than thirty years when delivered.

As has been stated above, the primiparous tuberculous women showed a greater mortality than the multiparous, following in this respect mortality among mothers in general. But the maternal mortality rates for the tuberculous women do not agree with the maternal mortality rates for the mothers in the general population in the matter of age at death. In his study previously mentioned Dr. Woodbury has shown that the maternal mortality rate has been lowest for the age-groups 20 to 24 and 25 to 29, in that order, and highest for the group under 15 years, followed closely by the mothers 45 years of age and over; "A considerable part, but not all of the greater mortality found for the youngest mothers" he ascribed to the "disproportionate number of primiparae" among them. Coghlan found in New South Wales that "except for the age group 15 to 19 the mortality rate increased markedly with the age of the mother among both the primiparae and the multiparae." But, while for mothers in general the lowest mortality rate is found from 20 to 24, among the tuberculous mothers the highest mortality rate is found at these ages. A study of the deaths from tuberculosis in the U. S. registration area shows that the same age-period, 20–24, is the one in which the death-rate from tuberculosis is highest among females, with the period from 25 to 34 years the next dangerous. A curve plotted to show the deaths at different ages of the tuberculous pregnant women would correspond in general to a curve plotted to show the deaths at different ages of all tuberculous women in the registration area. However, a consideration of the deaths by age according to whether the patient was diagnosed before, during, or after her pregnancy reveals some interesting facts.

Only one woman of the 27 under twenty-five years of age died in the group diagnosed before pregnancy, and she, an inactive case, died after a Caesarean section. Five of the 25 women under twenty-five who were diagnosed during pregnancy, or one-fifth, died. But of 81 women this same age who were diagnosed after confinement the number who died was 29, or 36 per cent. Since among the women diagnosed respectively before, during, and after pregnancy, the proportion who have died in

each of the age-groups under twenty-five years corresponds very closely, if not exactly, with the proportion who have died of those of all ages diagnosed in the same period, it is clear that the chances of a woman's living or dying are more closely related to whether the diagnosis of tuberculosis is made before, during or after her pregnancy rather than upon her age, itself.

When the parity of the mother is studied together with her age it is seen that for those diagnosed *before* pregnancy the mortality was greatest in primiparae from 25 to 29 years old. In the other age-groupings of mothers diagnosed before pregnancy and in those diagnosed *during* pregnancy the number of deaths is too small to show anything of significance in the way of a correlation of age with order of birth. The woman showing the greatest mortality according to the data of the study was the primipara diagnosed as tuberculous *after* her pregnancy. And for her the greatest danger as evidenced by the incidence of deaths was in the years from 25 to 29 at the time of childbirth and the next greatest from 20 to 24, half of those in the former age period and 49 of those in the latter losing their lives.

Thus far in this report, as later on, it has been deemed advisable to place the emphasis upon mortality rather than upon any change for better or for worse or upon no change in the patient's condition because death is a condition about which there can be no doubt, while different diagnosticians might disagree with the findings based upon the histories of some of the patients alive when last known.

Since the period when diagnosed rather than the age at diagnosis appears to be the determining factor in the patient's progress, it is unfortunate that such a large percentage of gravid tuberculous women are not treated for tuberculosis until after their confinement. It should be kept in mind that according to the figures of this study twelve out of thirteen women, irrespective of their stage at diagnosis, diagnosed before a pregnancy, survive for at least one year after confinement; four out of five diagnosed during pregnancy so survive; but only two out of three do so of those not diagnosed until after delivery.

COUNTRY OF BIRTH

This study was limited, as stated above, to white women solely. Such a limitation was decided upon at the outset in view of the well-known fact that the average life of the tuberculous Negro woman after

she has been attacked by the disease is very much shorter than that of the white tuberculous woman and that in consequence the inclusion of any number of Negro women in the group studied would tend to make the findings misleading.

The mothers of the study were almost equally divided between those born in the United States and those born elsewhere, the former numbering 173 and the latter, 174. Two were of unspecified parentage. Of those born in this country 94 were the children of native parents, and 19 were of Polish, 18 of German, 5 of Canadian, 14 of mixed native and foreign, 13 of other foreign, and 10 of unspecified or unknown parentage. Among those born outside the United States 51 were from Poland, 17 each from Russia and Italy, 14 from Austria, 12 from Canada, 11 from Hungary, 9 from Rumania, 7 from England, 5 from Greece, 9 from Syria, Armenia and Turkey, and 22 from other foreign countries.

Whether it is that fewer native-born tuberculous women knew they were tuberculous when they became pregnant, or that fewer became pregnant when they knew they were tuberculous, the fact remains that of the 136 women diagnosed before they became pregnant only 56 were native-born while 79 were foreign-born, and the birthplace of one was not stated. Inasmuch as the women diagnosed after confinement included 90 born in the United States and only 57 born elsewhere (the birthplace of one other was unknown), the correct conclusion would seem to be that fewer native-born women knew they were tuberculous when they became pregnant. Of the women diagnosed during their pregnancy 27 were native and 38 foreign-born. In the women of the study those born in the United States of parents born in the United States present the poorest story so far as the time of diagnosis is concerned. Of their number only 20 were diagnosed before pregnancy, and 18 during pregnancy, but 55 after confinement One would naturally expect more intelligent action from this group. In sharp contrast to them are the Russians, all but three of them Hebrews, of whose number 16 were diagnosed before and one during pregnancy, and none after delivery. Not far behind the Russians were the Austrians of whom 11 were diagnosed before, 1 during, and only 2 after pregnancy. The Polish distribution followed rather closely that of the entire group, with 20 diagnosed before, 12 during and 19 after pregnancy. None of the Greeks was diagnosed until after impregnation, one not until after delivery. Among the Hungarians, Rumanians and the "other foreign" the diagnosis was made predominantly before pregnancy; among the

English, during pregnancy; and among the Italians, "Syrians, Armenians, and Turks," and among the Canadians, after delivery.

The small number of patients born in each of the several countries represented in the study has made it impossible to draw any definite conclusions as to the varying effects of pregnancy accompanied by tuberculosis upon women of specific nationality. Certainly no special differences ascribable to racial stock were evident in the course taken by the disease of the women diagnosed before impregnation, for no country contributed more than two deaths among the women diagnosed then. Among the Polish and those born in the United States of native parents, each including 20 patients diagnosed before pregnancy, only one death apiece had taken place within a year from the time of delivery. But it does seem worth noting that the five native-born women who died, of the 18 such diagnosed during pregnancy, were all children of parents born in the United States, and that of the eight foreign-born, diagnosed at this time, who died, three were Canadians, no other country being represented by more than one even though Poland had 12 patients and Canada only 4.

The mortality among those diagnosed after confinement was about the same for the native-born and for the foreign-born, each considered as a group. But differences existed within the groups. Fourteen deaths occurred among the 55 patients born in the United States of native parents. Nine of the 19 Poles died. Without larger numbers upon which to premise conclusions the correlation is not clear between the nationality of the women born in other countries and the course taken by their disease. Of those women diagnosed tuberculous after their confinement relatively more of those born in the United States, and especially those of native parentage, were in the far-advanced stage of the disease when diagnosed than was the case with the foreign-born, the per cents far advanced being respectively 33, 38, and 25. Only twenty-one per cent of the Polish diagnosed after delivery were far advanced as compared to the thirty-eight per cent of the native-born.

All except three of the Russians were Hebrews, as has been stated above. Only four other Jews appeared in the study, of whom two were born in Rumania, one in Hungary and one in the United States of unspecified parentage. Two only of the Hebrews died, one diagnosed before and one during pregnancy, and in each instance the death occurred following a Caesarean section, the former a few hours afterward and the

latter ten weeks after the operation which had been performed at eight months of gestation.

SANATORIUM EXPERIENCE

A study of the sanatorium experience of these tuberculous mothers reveals that it has been far from adequate. One hundred and sixty-two, or 46 per cent of the whole 349, so far as known received no treatment for their tuberculosis in a hospital or sanatorium. For 58 of the 188 who did receive such care its duration was less than six weeks. Thus of the entire group only 123, or about one-third, were known to have had as much as six weeks' institutional treatment; for 6 the extent of care was not known. This sanatorium care has included any given up to the last date the case was known, not necessarily by the end of the first year after the termination of the pregnancy. Many more of those diagnosed after delivery were hospitalized than of those diagnosed before or during pregnancy, the percentages being 66, 46, and 42 respectively.

Hospitalization of the women of the study diagnosed *after* confinement appears on the whole to have been of little value, due largely to their advanced stage of disease and the shortness of time in the institution. More than a third of the number hospitalized, 35 of the 97, received care for less than six weeks in a hospital or sanatorium. In fact, some received care for only a few days or less. When the patients became dangerously ill, when obviously beyond the possibility of benefiting much, if any, from sanatorium care, they were apt to be taken to an institution where in many cases they died. This is probably the reason a very slightly higher percentage of those hospitalized died than of those not. Of those cared for less than six weeks half died; of those cared for at least six weeks but less than six months, one-third died; and only one died of the nineteen who survived long enough to be under care for at least six months. Fourteen of those hospitalized for less than six weeks were far advanced, 14 were moderately advanced, and 7 were minimal cases, of whom eleven, five, and one, respectively, died.

Likewise among those diagnosed *during* pregnancy who were given sanatorium or hospital care the death-rate was higher than among those who were not, but again this may be explained by the shortness of time under care and certain other factors. The actual number of hospitalized patients, diagnosed during pregnancy, who died was eight. Only one, a moderately advanced case at diagnosis, received as much as three months'

care; she died during the period of gestation. Three patients who died received care only after delivery, one far advanced, for five days; one minimal case at diagnosis, for one day; and one moderately advanced, for seven or eight weeks. The two who, aside from the one first mentioned, received care during the pregnancy alone included a moderately advanced patient who died of smallpox during pregnancy after two weeks' hospitalization and one who was hospitalized for seven or eight weeks. The others, one moderately advanced and one minimal at diagnosis, who died received care both during and after pregnancy, but for less than eight weeks each.

The histories of the nine women diagnosed as tuberculous *before* pregnancy, who spent some time in a sanatorium or hospital for tuberculosis, and who died before or in less than a year after delivery, present some interesting facts. Only three, one moderately and two far advanced, had received sanatorium care during the pregnancy; they had all been in institutions before pregnancy, also. Two of the three left the sanatorium early in the period of gestation; the third, hospitalized for a total of twenty-eight months, spent three months during pregnancy and was confined in the hospital where she died of diphtheria. The sanatorium care for three of the deceased all preceded pregnancy. One of the three, a minimal, apparently arrested case, died after a Caesarean section, her lungs remaining inactive at the time of her death; another, moderately advanced, spent only two weeks in a sanatorium just prior to impregnation and died during pregnancy; the third, also moderately advanced, under care for less than a month in the sanatorium, died ten days after the birth of her child in the obstetrical pavilion of the hospital where she had been for five weeks before the delivery. Three of the deceased were hospitalized for their tuberculosis only after confinement, one just for the ten days between her delivery and death, one for seven weeks, and one for seven months. Only one woman of all those diagnosed before pregnancy was under the supervision of both a tuberculosis specialist and an obstetrician during the later months of gestation and the delivery.

ATTENDANT AT BIRTH

Nothing of import to the solution of the problem under discussion appears from a consideration of the attendant present at the delivery of these tuberculous women. Information on this point was obtainable

for only about four-sevenths of the cases. Midwives were known to have attended only fifteen patients, of whom seven had been diagnosed before and five during pregnancy and three were diagnosed after confinement. Each of the last three noticed the first symptoms of tuberculosis some time after their delivery. Of the women diagnosed before pregnancy 38 were known to have been delivered in hospitals and 29 by physicians at home. Of those diagnosed during pregnancy 20 were recorded as delivered in hospitals and 22 by physicians at home. Of those diagnosed after confinement 26 were delivered in hospitals, in which institutions two of the women were diagnosed for the first time, and 47 by physicians in their homes. Of course no attendant was present when a few women miscarried and when one or more were delivered at a later period of gestation. In general, the earlier the patient was diagnosed tuberculous the more apt she was to be delivered in a hospital rather than at home.

OTHER DATA RELATED TO CHILDBIRTH

It is obvious that, if in a record study such as this information regarding the attendant at birth was in so many instances unobtainable, data on other points intimately related to the subject, such as the method of delivery, complications of the labor itself, of lactation, and any others of the pregnancy and puerperium, would be so lacking as to preclude discussion.

TUBERCLE BACILLI IN THE SPUTUM

In and of itself the record of the presence or absence of tubercle bacilli in the sputum of these tuberculous mothers means little. No record of a sputum examination was found in the case of 67 of the 349 patients. One hundred and thirty-four of the others were reported as having a positive sputum at some time and 150 as not. It is probable that a number in the negative-sputum group actually expectorated tubercle bacilli during the course of their illness even though there is no record to this effect. In general, as might be expected, the patients recorded as having expectorated tubercle bacilli have been those in whom the disease has been at least moderately advanced, and, therefore, those among whom the greater mortality would naturally occur. In the group of 136 patients diagnosed before conception, only 29 were recorded as having tubercle bacilli in their sputum, 82 as not having them, and for 25 there was no record. Of the 65 mothers diagnosed during pregnancy

20 were recorded as having a positive and 35 a negative sputum, and for 10 there was no record. Of the 148 diagnosed subsequent to delivery 85 were known to have had a positive sputum, and 33 a negative, and for 30 the character of the sputum was not of record.

WASSERMANN REACTION

It was recognized that syphilis might have been a complication in the pregnancies of the patients under consideration, and an attempt was made to obtain information as to the extent of its presence as indicated by a positive Wassermann reaction, but the data obtainable were too meagre to warrant discussion.

PLAN FOR FURTHER RESEARCH INTO RELATION BETWEEN PREGNANCY AND TUBERCULOSIS

When research into the relation between pregnancy and tuberculosis was first considered by the National Tuberculosis Association, it was hoped that pertinent histories of at least two thousand women might be obtained. It was contemplated that field work by a member of the staff in connection with the study, first undertaken in Detroit, might be extended to other large cities. But it was found that the length of time required, and incidentally the expense consequent upon such a long period of study, was too great for the research to proceed in this fashion. Furthermore, it was believed that possibly a more accurate picture of the relation between pregnancy and tuberculosis might be obtained if histories were to be taken with both these conditions in mind concurrently with the progress of the case. Consequently a new plan has been evolved in which it is hoped a considerable number of physicians will be sufficiently interested to coöperate. A simple record form (see p. 143) has been drawn up and printed which covers the essential measurable factors bearing upon the problem. Likewise a set of simple instructions in how to fill in the form has been prepared so that the coöperating physicians will interpret the items called for in like fashion. The aim is for each physician interested to fill out as fully as possible a record for *each and every* tuberculous married woman coming under his care, whether the woman is pregnant or not when first seeking his advice; for him to enter on the form as time goes on any change in her condition with respect to the tuberculous disease or maternity; and when the case has been finally closed by the physician, either for death or other cause, for him to send

STUDY OF TUBERCULOUS MOTHERS

NATIONAL TUBERCULOSIS ASSOCIATION
370 Seventh Avenue, New York City

1. Place ____ 2. Address of Patient ____ 3. Dates under Supervision ____

4. Name of Patient ____ 5. Race ____ 6. Date of Birth ____

7. Married, Single, Widowed, Divorced, Separated (Check) 8. Country of Birth (a) of Patient ____ (b) of Parents ____

9. Date and Cause of Onset according to (a) Patient ____

____ (b) History and Examination ____

10. Date of Diagnosis ____ 11. Type of TB ____ 12. Stage ____ 13. Sputum ____

14. X-Ray ____ 15. Wasserman ____

16. Sanatorium Experience (a) where ____ (b) Dates ____

____ ____

____ ____

17. Clinic Experience (a) where ____ (b) Dates ____

____ ____

18. Pregnancies

a Order	b Name	c Period of gestation	d Date of birth	e Place of delivery	f Attendant at birth	g Method of delivery	Complications of h Pregnancy	i Labor	j Puerperium	k Lactation
1st										
2nd										
3rd										
4th										
5th										
6th										
7th										
8th										
9th										
10th										
11th										
12th										

19. Date of Marriage ____ 20. Notes ____

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21. Co-operating Physician ____

April, 1926

the finished record to the National Tuberculosis Association. It is hoped that thus in time may be assembled a number of comparable case histories sufficiently large to warrant the basing of definite conclusions upon them. Under such a scheme the histories of those women with no related pregnancy will be used as controls, that is, they will serve as a standard with which the histories of the pregnant women may be compared. Cases known to obstetricians can be compared with those known to the tuberculosis clinicians and with those known to the general practitioner. The lone case of the country physician will be of use as well as the many of the city clinician. It may be five years or more before a desirable number of records have been assembled. A number of the record forms are now ready for distribution, in fact about eight hundred have already been sent to physicians who have asked for them, and more will be printed as needed. It is earnestly desired that a large number of physicians will be interested sufficiently in this important question generously to join with the National Tuberculosis Association in this research looking toward its solution.

SUMMARY OF FINDINGS

1. A comparison of the condition of the 160 women whose pregnancies accompanied or immediately preceded their tuberculosis with that of their close controls at one year and at two years after diagnosis (and in the case of the pregnant women, after conception or confinement) leads to the conclusion that pregnancy had no appreciable bearing upon the progress of the tuberculous disease.

2. The earlier the 349 mothers of the study were diagnosed with respect to their pregnancy, the less hazardous the latter was for them. Less than one in twelve of the women diagnosed before gestation was dead a year after its termination; one in five of the women diagnosed during pregnancy was dead, and one in three of those diagnosed after delivery.

3. The number of pregnancies of less than full term found during the study is too small for a discussion of them to be of real value.

4. The order of the pregnancies of the whole group of tuberculous mothers approximated very closely the order of birth of the children born to white Michigan mothers during approximately the same period, but there were important differences within the group. Primiparae constituted only fifteen per cent of the women diagnosed before pregnancy, but twenty-one per cent of those diagnosed during pregnancy and thirty-two

per cent of these diagnosed after confinement. The highest mortality among the tuberculous women of the study was suffered by those pregnant for the first time, the danger of primiparity among the tuberculous being similar to that among the mothers in general.

5. The ages of the entire group of tuberculous mothers at the close of their pregnancies closely paralleled the ages of all white mothers in Michigan at the birth of their children during much the same period. But the younger mothers were being diagnosed later with respect to the pregnancy than the older ones. Only twenty per cent of those diagnosed before conception were under twenty-five years of age, while of those diagnosed after parturition 55 per cent were.

6. The maternal mortality rates for the tuberculous women of the study do not follow the maternal mortality rates for mothers in the general population in the matter of age at death. Instead they correspond on the whole with the deaths at different ages of all tuberculous women. The age-period, 20 to 24 years, in which the highest mortality among the tuberculous mothers of the study occurred is also the one in which the tuberculosis death-rate among females in the registration area is highest but the one in which the mortality rate for all mothers is the lowest.

7. The women of the study latest with reference to pregnancy in being diagnosed tuberculous were those born in the United States of native parents, of whom about three-fifths were not diagnosed until after confinement. In contrast all except one of the seventeen Russians were diagnosed before pregnancy. The small number of patients born in each of the countries represented in the study has made it impossible to draw any definite conclusions regarding the effects of pregnancy upon tuberculous women of specific nationality.

8. Only about one-third, 123 of the 349, of the entire group of tuberculous pregnant women were known to have had as much as six weeks' sanatorium treatment. Many more of those diagnosed after delivery were hospitalized than of those diagnosed before or during pregnancy. Much of the hospitalization was of little value because it came when the tuberculosis was too far advanced. Only one woman of those diagnosed before pregnancy was under the supervision of both a tuberculosis specialist and an obstetrician during the later months of gestation and the delivery.

9. Sufficient information was not obtainable regarding the attendant at birth, other data associated with childbirth, the presence or absence of

tubercle bacilli in the sputum, and Wassermann reactions to warrant comment.

10. In the belief that a better picture of the relation between pregnancy and tuberculosis might be obtained if histories were to be taken with both these conditions in mind concurrently with the progress of the case, a new plan of research has been evolved in which it is hoped a considerable number of physicians will be sufficiently interested to coöperate. The scheme is for each physician interested to fill out as fully as possible a uniform record form for each and every tuberculous married woman coming under his care, entering on the form as time goes on any change in her condition, and when the case has been closed for the physician to send the completed record to the National Tuberculosis Association.

CONCERNING THE TUBERCULOUS NATURE OF PLEURISY FROM THE LIFE INSURANCE STANDPOINT

H. B. ANDERSON[1]

With the exception of pleurisy the direct result of trauma, the weight of authority is strongly in favor of regarding all pleurisies as secondary. Even in the case of traumatic pleurisy, the injury usually only produces a *locus minoris resistentiae* for the localization of an infection already existent elsewhere in the body, or awakens into activity a latent tuberculosis of the pleura itself. Rheumatic pleurisy has often been cited as a typical example of primary pleurisy, but few clinicians have seen cases in which such a diagnosis can be made with assurance, and, if a primary rheumatic pleurisy ever occurs, it is so infrequent that it would be better to discard the term altogether.

Pleurisy following exposure and chill—the *pleurisie à frigore* of the older writers—is now generally regarded as secondary to another infection, usually tuberculosis. This is the form of pleurisy to which the term *primary* is usually applied clinically.

The text-books commonly in use when I was an undergraduate thirty-five years ago,—Flint, Roberts, Hilton Fagge and even the first edition of Osler,—usually attributed primary pleurisy to cold, injury, rheumatism or other cause, without special reference to its being a common manifestation of tuberculosis. This had been the teaching from time immemorial. Laennec cited, as occasional causes, inclemency of the weather, cold, violent exercise, metastasis of gout, rheumatism or cutaneous eruptions, blows on the chest and fractured ribs, though he does mention "a slender frame and narrowness of the chest" among the predisposing causes.

Graves in 1842 stated that "it is a law of pathology that if a pleurisy appear on one side of the chest and some time afterward show itself in the other, it in all likelihood is dependent upon tubercles. This law of double pleurisy was discovered by Louis and in most cases must be relied upon with certainty."

In 1886 Kelsch and Vaillard, in an analysis of 113 cases of acute

[1] Medical Director, Imperial Life Assurance Co., Toronto, Canada.

pleurisy, found 82 per cent to be tuberculous and they concluded that "ordinary pleurisy is only a manifestation of local tuberculosis." Landouzy, in a paper in the *Revue de Médicine*, in 1886 stated that from 70 to 75 per cent of all cases of acute pleurisy are tuberculous; and the same year Germain Sèe expressed the opinion that "so called pleurisy from a chill is only tuberculous pleurisy, the nature of which has been misunderstood." This recognition by French clinicians of the tuberculous nature of ordinary pleurisy, was accepted and confirmed by German, English and American clinicians, and the lapse of time and further investigations have only served to establish more fully the correctness of their views. It represented a striking, and from the clinical standpoint, a most important change of front regarding the significance of pleurisy.

Vincent Y. Bowditch, in an analysis of his father's cases from 1849 to 1879, concludes that the *Bacillus tuberculosis* is the causative agent in a very large proportion of cases of serofibrinous pleurisy, and this is true when the attack is apparently simple, idiopathic, and attributed to chill; and Osler (1892), through he still believed that primitive pleurisy occurred as "an independent infection following cold or exposure and is not uncommon in perfectly healthy individuals," began to show the influence of the teaching of the French school: "I confess that the more carefully I have studied the question, the larger does the proportion appear to be of primary pleurisies of tuberculous origin."

The present attitude regarding pleurisy is reflected in the opinions expressed in personal communications from well known authorities herein briefly summarized:

Bray believes "that for insurance purposes all idiopathic pleurisies should be considered as tuberculous." Couillard is inclined to believe that the vast majority, perhaps 90 to 95 per cent, of primary pleurisies are due to tuberculosis. Kinghorn "has no doubt whatever that ordinary pleurisy should be regarded as evidence of tuberculosis." A. F. Miller's "impression is that a large proportion of so-called idiopathic pleurisies are tuberculous and in sero-fibrinous pleurisy that comes on insidiously—it is almost certain to be tuberculous." Parfitt thinks an insidious pleurisy with effusion, not otherwise explained, is generally to be accepted as tuberculous. Pritchard believes "a so-called primary pleurisy should be considered tuberculous." Pottenger "has no doubt but insurance companies should consider primary pleurisy as tuberculous." Peers, from an experience of over twenty years, concludes "that pleurisies with a serous effusion are practically always tuberculous and feels very strongly that pleurisy should be considered tuberculous unless

proved otherwise." Stewart "is of opinion that the more complete the investigation and the more searching the history, the more definitely the statement would be made that pleurisy with effusion is tuberculous in almost all cases." He would be inclined to cast doubt upon a pleurisy being primary even when it seems to be a bolt from the blue.

Sergent and Pruvost have recently gone so far as to classify all ordinary pleurisies as tuberculous, and though this may be considered a somewhat extreme view, few will dissent from the opinion that dry or serofibrinous pleurisy, acute or chronic, is to be considered as tuberculous, unless tuberculosis can be absolutely excluded. In a case, therefore, of common, so called idiopathic or primary pleurisy, the burden of proof lies on the practitioner who concludes that it is nontuberculous and such a diagnosis places upon him a serious responsibility.

The tuberculous nature of pleurisy with serous effusion is more generally accepted than that of dry pleurisy. Paterson's interesting experiments led him to conclude that the serous effusion is an allergic phenomenon, occurring only in persons already sensitized by the presence of tubercle elsewhere in the body, usually pulmonary or lymphatic. According to this authority, pleural effusions are not due to primary infection of the pleura but to infection in a system already tuberculous, and after the pleurisy has subsided we must recognize that the patient is still tuberculous. Whether the effusion is serous, turbid or purulent depends upon the number of bacilli.

While it seems probable that a larger percentage of clinically dry pleurisies are nontuberculous, yet it must not be overlooked that this more favorable view is partially due to the fact that this group includes an uncertain percentage of cases of intercostal neuralgia, pleurodynia, myalgia and herpes zoster, incorrectly diagnosed as pleurisy. Bandelier and Roepke, Lord, Emerson, Carmichael, Sergent and Pruvost, Capps, and others believe that ordinary dry pleurisies are usually tuberculous and with this view I am fully in accord. West emphasized the distribution of the pleurisy, and that if it is general, apical, bilateral or patchy it is more likely to be tuberculous. The presence of fever, even of a slight fever, is a crucial point in distinguishing cases of chest-pain due to pleurodynia, myositis, etc., from pleurisy and the importance of obtaining the evening temperature should always be borne in mind.

One cannot combat too strongly a tendency to overlook the significance of an attack of dry pleurisy because it is of brief duration. It is the nature of the underlying cause, not the length of the attack,

which is most significant, and one frequently has seen a case, lasting only two or three days and not confining the patient to bed, the precursor of pulmonary tuberculosis.

Confirming Parrot's investigations (1876), Albrecht, Küss, Ghon and others have concluded that air-borne infection accounts for perhaps 95 per cent of cases of tuberculosis in children.

This aerogenous infection produces a primary pulmonic focus, varying in size from a pinhead to a hazel nut, with subsequent similar but more extensive involvement of the tracheobronchial lymph nodes. The primary focus is usually subpleural, and may either heal, petrify or caseate. In 67 per cent of Ghon's autopsies there was pleural involvement, generally slight, on the same side as the primary focus and usually over the corresponding lobe. Cases, in which the primary lung focus and tracheobronchial lymph node involvement heal, indicate or develop a high grade of immunity to subsequent tuberculous infection and after a sufficient lapse of time are probably better risks than children who have never developed an immunity from previous infection.

Paterson and others believe that a pleurisy with effusion indicates at least a relative immunity, and this perhaps accounts for the favorable outlook in cases that have recovered and remain well after a lapse of some years. During the Great War it was noted by German observers that recruits from isolated mountain districts, who had never been exposed to tuberculous infection and therefore had acquired no active immunity, readily developed infection when exposed and the disease ran an unfavorable course. In adults, as in children, a limited tuberculous focus, which has completely healed and with the individual's general condition satisfactory after a lapse of five or more years, may be a better risk than if in one who has never been infected.

Calmette is not in accord with the widely accepted views of Ghon and others that aerogenous infection is the common mode in children, but on the contrary believes that infection usually occurs through the alimentary mucous membranes, and thence, by way of the blood and lymph-stream, produces pulmonary and lymphatic infection.

As a result of "the work of Landouzy, Kelsch and Vaillard, Netter, Weischselbaum, Gombault and Chauffard, Le Damany, Prinz Ludwig and others," Calmette believes that the pleurisies are almost always of tuberculous origin, but tubercles of the pleura, when not concomitant with widespread lesions of the lung, tend generally to become sclerotic.

India-ink, injected into the tonsils, will pass through the lymphatics

and stain the pleura,[2] and it is well known that coal dust will similarly pass through the lymph channels and cause pleural staining. There is, therefore, no anatomical reason why infection may not pass through the blood- or lymph-vessels and produce a pleurisy without coincident pulmonary involvement.

Luetscher's bacteriological study of nontuberculous respiratory infections shows that while the streptococcus predominates in tonsil and head infections, pneumococci account for 62.5 per cent and the influenza bacillus for 28.5 per cent of infections of the lungs and bronchi. It seems quite probable that pathogenic microörganisms may be transmitted through the lymph-stream from the tonsils, teeth, bronchi, etc., and set up a plastic adhesive or a serous, though often clinically latent, pleuritis. At autopsy healed miliary tubercles are occasionally found scattered over the visceral pleura, in the absence of evidences of pulmonary tuberculosis.

Adhesive pleuritis may similarly occur as part of the clinical picture of pneumonokoniosis even in cases uncomplicated by tuberculosis. That mild, latent, or nonprogressive adhesive pleurisy may result from infection, mechanical, chemical or other irritation, without pulmonary infection, is suggested by the frequency with which pleuritic adhesions are found at autopsy compared with the infrequent occurrence of pleurisy clinically. Lord states that in 215 autopsies in the Massachusetts General Hospital pleuritic adhesions were found in 74.4 per cent of cases, whereas pleurisy had occurred clinically in only 2.4 per cent of 18,543 medical cases. Fraley's statistics for the Pennsylvania Hospital show a history of pleurisy in 2.5 per cent of 19,396 cases.

In the Lumleian lectures, 1885, Sir Andrew Clark discussed primitive dry pleurisy as a clinical entity. The condition, he believed, developed as a primary disease of the pleura, and often produced great thickening, and by extension involved the interstitial tissue of the lungs, leading to fibrosis. While later investigators undoubtedly would classify most of these cases as tuberculous, and some as syphilitic, yet it is not unreasonable to believe that a nontuberculous dry adhesive pleurisy may occur, and the facts just mentioned strengthen that belief. In many instances, however, the adhesive pleurisy is found only postmortem and represents a pathological rather than a clinical condition. This latent pleurisy, therefore, does not present itself as an insurance problem.

[2] Grober, Deutsch. Arch. klin. Med., 1902, quoted by Calmette.

The latter is concerned with clinical pleurisy, especially the common acute or insidiously developing subacute dry or serous pleurisies, not associated with demonstrable disease in the lungs or elsewhere.

It is well known that a secondary pleurisy may result by extension from a tuberculous rib, spinal caries, mediastinal tuberculosis, aneurysm or malignant disease, or be associated with pulmonary infarction or abscess. Wharton and Pierson, Gwyn, and others have emphasized the importance of minor emboli, detached from femoral or abdominal thromboses, as the cause of postoperative pleurisy; and, lastly, a well-recognized group of pleurisies is that occurring late in the course of Bright's disease, cardiac disease, cirrhosis of the liver, the leukaemias, Hodgkin's and other chronic diseases. As Osler points out, however, the latter are frequently tuberculous.

Pleurisy is a usual accompaniment of pneumonia and is not an infrequent complication of other systemic infections, such as influenza, septicaemia, typhoid fever, or the acute infectious fevers and rheumatism. The possibility that a pleurisy, occurring late in the course of an acute infection or during convalescence, is tuberculous, should never be overlooked, the lowered resistance of the patient from the primary disease presenting the morbid opportunity for the awakening of a previously latent tuberculosis.

Pleurisy, as before stated, may be secondary to focal infections of the teeth and tonsils, and, as some authorities believe, of bronchitis and bronchiectasis. Patzetakis of Athens (quoted by Hoover), in 51 cases of bronchitis in a military hospital at Athens, found fluid on aspiration in 38, the amount varying from a few to 50 cc. There was no evidence of coincident pulmonary infection, and the presence of the fluid did not influence the course of the disease.

In Hedges's 130 cases of primary (?) pleurisy with effusion, the subsequent course of which was followed for seven years, 40 per cent had developed tuberculosis; in H. P. Bowditch's 90 cases of pleurisy, observed 1849–1879, 30 had developed or died of phthisis; in R. C. Cabot's 300 cases of pleural effusion in the Massachusetts General Hospital, the subsequent history was traced in 221 cases for a period of five years, at which time 117, or 53 per cent, were dead or had phthisis, and 96 were well; of Hamman's 562 collected cases of pleurisy, 167, or 30 per cent, developed tuberculosis.

Hospital statistics no doubt reflect a more unfavorable experience than would obtain in the general population, and especially since the

usual tuberculous nature of pleurisy has been generally recognized and the disease properly treated.

Graham recently reported 56 cases of pleurisy with effusion (1914 to 1923), in which 36 cases were traced from 3 to 5 years. Thirty-one were quite well, and only five had a recurrence of pleurisy or developed tuberculosis elsewhere in the body. In all but one case the subsequent tuberculosis manifested itself within one year after the attack of pleurisy.

It should be emphasized that the rigidly selected cases of pleurisy, accepted by the insurance companies, no doubt reflect a much more favorable experience than that of pleurisies in general.

Clinical experience, as well as statistical data, bear out the attitude of insurance companies that the danger period in ordinary pleurisy is in the years immediately following the attack, and during this period, at least for the first year or two, the lives are either uninsurable, or accepted only after rigid selection, and with provision for a high mortality experience. My own company accepts some of the most favorable cases after a year, but usually after two years, from the attack, on the endowment plan with liens of from 45 to 60 per cent.

In the favorable cases there is a gradually decreasing risk, so that after five years, and especially with applicants over 30 years of age, whose general condition, family history, build, weight, habits and occupation are satisfactory, the applicants are accepted at standard rates.

After a further lapse of five to ten years, even family history and moderate underweight may be discounted to some extent, as the compensating favorable influence of underweight at older ages gradually over-balances the danger from tuberculosis, and after forty years of age give a favorable mortality experience.

However, it should always be borne in mind, especially in applicants with a family history of tuberculosis, with poorly formed chests and if the underweight is greater than before the attack, if the tendency is to further decrease, or if weight falls below the family tendency, that the failure to regain or increase in weight may be due to the persistence of a clinically latent, but by no means negligible, systemic tuberculosis.

In such cases of considerable underweight it is doubtful whether the favorable influence of time ever overbalances the danger from recrudescence of the disease, so as to permit of such lives being accepted as standard risks or granted disability benefits.

In cases of pleurisy remaining underweight after the time when favorable cases would have completely recovered, regained or increased

their best former weight, there is always a danger of tuberculosis appearing in some form, somewhere in the body. The following case represents the type I have in mind:

W. S.; age 55; 5 feet, 9 inches in height; bricklayer; no tuberculosis in family; maximum weight, 155. Thirty years ago he had pleurisy with effusion; good recovery and regained weight, but only to 140 pounds. He consulted me ten years ago with an ischiorectal abscess, chronic and evidently tuberculous. After the abscess healed, he regained his health and weight to 140 pounds; he felt well and lost no time at his trade, but in recent years he again began to lose weight slowly, until he weighed only 129 pounds. He consulted me recently and I found that he now has double tuberculous epididymitis. The point that I wish to emphasize is that a clinically latent systemic tuberculosis persisted after the pleurisy and probably accounted for his remaining underweight.

The following is another case in which 11 years' lapse of time and absence of symptoms hardly qualify the patient for standard insurance:

Age 30; 5 feet, 9½ inches; weight, 138 pounds. He gave a history of dry pleurisy in 1916, six months' duration; in the hospital for three months with a mild fever; at present there is very slight limitation of movement of the upper left chest, but otherwise there is no evidence of disease and his general condition is good. His maximum weight before the pleurisy was 156; his lightest weight was immediately after the pleurisy, namely 105. The family history shows no cases of tuberculosis and does not show any tendency to underweight, although they are all spare. The unfavorable features are the severity of the attack and that he is still 18 pounds below his best weight before the attack.

In insurance we have obviously to deal with a history of pleurisy in the past rather than with the active presence of the disease. The pleurisies, associated with chronic diseases and cachexias before mentioned, represent uninsurable lives and therefore fall outside the limits of the present discussion.

Of the cases of pleurisy associated with pneumonia, influenza and other acute infections, the history obtained of the symptoms, course and duration of the disease is usually so definite that no difficulty is presented in reaching a conclusion as to the diagnosis, though a history of pneumonia, in which the patient was only confined to bed for a few days or in which the illness was unduly prolonged or atypical, should always be regarded with suspicion.

Height	5-0	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6-0	6-1	6-2	6-3
Mean weight	131	131	133	136	140	144	148	152	157	162	167	172	178	185	192	200

	Age	Years elapsed since date of attack								
		2	3	4	5	6	7	8	9	10
− 40 lbs.	15	120	105	95	85	75	70	65	60	55
	20	115	100	90	80	70	65	60	55	50
	25	105	95	85	75	65	55	50	45	40
	30	95	85	75	65	55	45	40	35	30
	35	85	75	65	55	45	35	30	25	20
	40	75	65	55	45	35	25	20	15	10
	45	65	55	45	35	25	20	15	10	5
	50	55	45	35	25	20	15	10	5	0
	55	45	35	25	20	15	10	5	0	0
− 25 lbs.	15	95	80	70	65	60	55	50	45	40
	20	90	75	65	60	55	50	45	40	35
	25	80	65	55	50	45	40	35	30	25
	30	70	50	45	40	35	30	25	20	15
	35	60	45	40	35	30	25	20	15	10
	40	50	40	35	30	25	20	15	10	5
	45	45	35	30	25	20	15	10	5	5
	50	40	30	25	20	15	10	5	5	0
	55	35	25	20	15	10	5	5	0	0
− 10 lbs.	15	65	50	40	35	30	25	20	15	15
	20	60	45	35	30	25	25	20	15	15
	25	55	40	30	25	20	20	15	10	10
	30	50	40	30	25	20	15	10	10	5
	35	45	35	25	20	15	10	10	5	5
	40	40	30	25	20	15	10	5	5	0
	45	35	25	20	15	10	10	5	0	0
	50	30	20	15	15	10	5	0	0	0
	55	30	20	15	10	5	0	0	0	0
+ 10 to + 15 lbs.	15	50	35	25	20	15	10	10	5	5
	20	45	35	25	20	15	10	10	5	5
	25	40	30	25	20	15	10	10	5	5
	30	35	25	20	15	10	10	5	5	0
	35	30	25	20	15	10	5	5	0	0
	40	25	20	15	10	5	5	0	0	0
	45	25	20	15	10	5	0	0	0	0
	50	20	15	10	5	5	0	0	0	0
	55	20	15	10	5	0	0	0	0	0

	Age	Years elapsed since date of attack								
		2	3	4	5	6	7	8	9	10
− 35 lbs.	15	115	100	90	80	70	65	60	55	50
	20	110	95	85	75	65	60	55	50	45
	25	100	90	80	70	60	50	45	40	35
	30	90	80	70	60	50	40	35	30	25
	35	80	70	60	50	40	30	25	20	15
	40	70	60	50	40	30	25	20	15	10
	45	60	50	40	30	25	20	15	10	5
	50	50	40	30	25	20	15	10	5	0
	55	40	30	25	20	15	10	5	0	0
− 20 lbs.	15	85	70	60	55	50	45	40	35	30
	20	80	65	55	50	45	40	35	30	25
	25	70	55	45	40	35	30	25	20	15
	30	60	45	40	35	30	25	20	15	10
	35	50	40	35	30	25	20	15	10	5
	40	45	35	30	25	20	15	10	5	5
	45	40	30	25	20	15	10	5	5	5
	50	35	25	20	15	10	5	5	5	0
	55	30	20	15	10	10	5	5	0	0
− 5 lbs.	15	60	45	35	30	25	20	15	10	10
	20	55	40	30	25	20	20	15	10	10
	25	50	40	30	25	20	15	10	10	5
	30	45	35	25	20	15	10	10	5	5
	35	40	30	20	15	10	10	5	5	5
	40	35	25	20	15	10	5	5	5	0
	45	30	20	15	10	5	5	5	0	0
	50	25	15	10	10	5	5	0	0	0
	55	25	15	10	5	5	0	0	0	0

To obtain rating for + 20 lbs. or over, add rating for + 15 lbs. to the rating for build and average family history.

	Age	Years elapsed since date of attack								
		2	3	4	5	6	7	8	9	10
− 30 lbs.	15	105	90	80	70	65	60	55	50	45
	20	100	85	75	65	60	55	50	45	40
	25	90	80	70	60	50	45	40	35	30
	30	80	70	60	50	40	35	30	25	20
	35	70	60	50	40	30	25	20	15	10
	40	60	50	40	35	25	20	15	10	5
	45	50	40	35	30	20	15	10	5	5
	50	40	30	25	20	15	10	5	5	0
	55	35	25	20	15	10	5	5	0	0
− 15 lbs.	15	75	60	50	45	40	35	30	25	20
	20	70	55	45	40	35	30	25	20	15
	25	60	50	40	35	30	25	20	15	10
	30	55	45	35	30	25	20	15	10	10
	35	50	40	30	25	20	15	10	10	5
	40	45	35	25	20	15	10	10	5	5
	45	40	30	20	15	10	10	5	5	0
	50	35	25	15	10	10	5	5	0	0
	55	30	20	15	10	10	5	0	0	0
0 to + 5 lbs.	15	55	40	30	25	20	15	10	10	5
	20	50	40	30	25	20	15	10	10	5
	25	45	35	25	20	15	10	10	5	5
	30	40	30	25	20	15	10	10	5	5
	35	35	25	20	15	10	10	5	5	0
	40	30	25	20	15	10	5	5	0	0
	45	25	20	15	10	5	5	0	0	0
	50	25	20	15	10	5	0	0	0	0
	55	20	15	10	5	0	0	0	0	0

The ratings in the accompanying table are recommended by the Committee of Medical Directors and Actuaries of the Canadian Life Officers Association for applicants with a history of pleurisy. They take into account the age of the applicant, the degree of underweight and the time that has elapsed since the attack of pleurisy. The ratings are intended for use in a numerical rating system and represent additions to a basic rating of 100 per cent for a normal risk.

CONCLUSIONS

1. Pleurisy occurs very rarely as a primary disease.
2. The frequent evidences of pleurisy found at autopsy, contrasted with the relative infrequency of clinical pleurisy, suggest that pleural adhesions are often the result of an inflammation that is clinically latent.
3. Ordinary pleurisy with effusion is practically always tuberculous.
4. Ordinary dry pleurisy is usually tuberculous, but this group includes a number of cases of pleurodynia, myositis, herpes zoster and intercostal neuralgia, and a number of cases secondary to focal infections, rheumatism, septicaemia, emboli, bronchitis, bronchiectasis, pneumonokoniosis, etc.
5. Pleurisy represents a relatively mild and curable phase of tuberculosis; recent statistics since the nature of the disease and its treatment are better understood show a much larger number of complete recoveries.
6. Recovered cases over thirty years of age, which have regained their normal weight, in which there is no family history of tuberculosis, and the applicant's weight does not fall below the family characteristic, after five years, may be accepted at standard rates.
7. A completely recovered focal tuberculosis in childhood provides an increased immunity against tuberculosis in later years.
8. Cases with a history of pleurisy, in which underweight persists or tends to increase, especially when there is a family history of tuberculosis, poor chest conformation, etc., represent a dangerous group which probably never become standard lives.
9. Occupation, habits and environment are important considerations in selecting risks.
10. In cases with a history of pleurisy, combinations of unfavorable features, such as younger ages, poor build, underweight, family history of tuberculosis, occupation, unsatisfactory habits, etc., are more serious than would be expressed by a summation of the impairments.

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ELECTROCARDIOGRAPHIC STUDIES IN PULMONARY TUBERCULOSIS

A Preliminary Report on 250 Cases[1,2]

SALING SIMON AND FELIX BAUM

The relationship between diseases of the heart and pulmonary tuberculosis has received but scant consideration in medical literature. The old teachings of Rokitansky that the presence of heart disease prevented or retarded the development of pulmonary tuberculosis are no longer held. It is true, however, that pulmonary tuberculosis rarely develops in the presence of mitral stenosis. Bohland (1) has observed, in some young individuals in whom mitral disease had existed for a long time, the later development of acute tuberculosis. Colthrop (2), examining the records of 1,097 postmortem examinations made between 1898 and 1919 at the London City Hospital for Diseases of the Chest, found only 29 in which pulmonary tuberculosis coexisted with valvular heart diseases (see summary, *Journal of the American Medical Association*, June 5, 1920, page 1606). James M. Anders (3), discussing the subject of tuberculous myocarditis, concludes that tuberculosis of the myocardium, which is invariably secondary to tuberculosis of the mediastinal lymph nodes, is more common than has been generally supposed. Anders furthermore maintains that myocardial tuberculosis is often secondary to tuberculous pericarditis. He states, however, that the clinical diagnosis in these cases is extremely difficult although it may be made under favorable conditions and after careful study.

In view of the difficulty of making a diagnosis of the existence of cardiac defects in cases of pulmonary tuberculosis with the usual methods of examination, it was considered advisable by the writers of this paper to employ the electrocardiograph in a study of some 250 cases of chronic pulmonary tuberculosis, in order to learn whether any light could be

[1] From the Medical Department, National Jewish Hospital, Denver, Colorado, and the Medical School, University of Colorado.

[2] Presented before the Clinical Section at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 27, 1927.

obtained on the subject. It was also thought that by means of the electrocardiograph certain effects upon the heart would result, following the use of artificial pneumothorax, thoracoplasty and phrenectomy, and that a definite relationship between valvular heart disease and pulmonary tuberculosis could be established.

It is a well-known fact that the shape of the heart conforms to the shape of the frame of the body. Contrast, for example, the asthenic and hypersthenic types. The thorax of the asthenic individual is long and flat, and the heart is suspended from the vessels at the base, the apex touching the diaphragm without resting upon it. The vertical position of the heart influences the electrocardiogram to a certain degree; and we often see present in the latter a right ventricular predominance or right axis deviation with a small *R* or even an inverted *R* in the first lead and a high *R* in the third lead, which is distinctly different from the physiological left ventricular predominance (left axis deviation) of the normal heart. In the hypersthenic type, with its relatively large heart which rests on the high diaphragm, we would expect to get a more pronounced left ventricular predominance or left axis deviation than is seen in the normal electrocardiogram.

Figure 1 represents a typically normal electrocardiogram. The *P* wave represents the auricular complex and the *QRST* the ventricular complex, which terminates with the *T* wave. The peak of the *QRS* precedes the ventricular contraction, whereas the *T* wave coincides with the height of the ventricular contraction and precedes the second sound of the heart. According to Pardee (4), there are four features in each wave that should be noted: first, the maximum height recorded in any one of the leads (voltage); second, the relation of the height and direction of the three views of the waves as given in the three leads; third, the forms of the wave or peak, whether sharp, rounded, notched, etc.; and fourth, the duration as measured by its straddle on the base-line of the record.

Figure 2 shows an X-ray (teleoroentgenographic) of the heart in an asthenic type of individual suffering from far-advanced pulmonary tuberculosis. We are all familiar with the description of the so called "drop" heart, or Kraus and Wenkebach's *Cor Pendulum*, but little is given in the literature about the electrocardiographic characteristics of such a heart. In our study of this type of heart we often found present an extremely low potential in either the first or third lead, as will be seen from figure 3.

Figure 4 shows an X-ray of the hypersthenic type of individual suffering from chronic pulmonary tuberculosis and aortitis. A slight tuberculous infiltration of the apex is seen, and the heart is enlarged to the left, resting on the diaphragm. The electrocardiogram (figure 5) of this case reveals a left ventricular predominance (left axis deviation) as is indicated by the inverted R (or long S[3]) in the third lead.

Figure 6 shows a case of far-advanced pulmonary tuberculosis, with cavity formation in the left upper lobe and a marked fibrotic cirrhosis of the left lung, with a number of pleural adhesions pulling the heart over to the left side. In such cases there is increased work thrown upon the right heart, and, from our autopsy findings, we know that such a heart commonly shows both a dilatation and hypertrophy of the right ventricle. We would, therefore, expect the electrocardiogram to show a right ventricular predominance (right axis deviation). The lantern slide shows this to be present, for we find the R wave inverted in the first lead and R_3 exceeding the height of the inverted R_1 (figure 7).

In a very interesting article, published by Boas and Mann (5), on the right ventricle in pulmonary tuberculosis, the authors found that of 97 patients with pulmonary tuberculosis 29 per cent had a right ventricular predominance (right axis deviation), 30 per cent left ventricular predominance (left axis deviation), and 41 per cent no predominance of either ventricle. Right ventricular predominance occurred more frequently in young than in old patients, whereas left ventricular predominance was more frequent in older patients. The authors also concluded that, contrary to necropsy findings reported in the literature, ventricular predominance is not more frequently found in patients with fibroid phthisis or with pleural adhesions than in other types of pulmonary tuberculosis. Our observations on 250 cases show only 10 per cent of right and 10 per cent of left ventricular predominance. Table 1 gives the height of the P, QRS and T waves in millimetres in the 250 tuberculous patients examined by us. It will be seen that the average measurements obtained in these cases do not differ essentially from those noted by Lewis in his 52 normal cases (table 1). Pardee's study of 26 normal cases (table 2) does not materially differ from our findings (table 2B), except that in many of our tuberculosis patients the P and T waves, which in Pardee's study were upward in leads I and II, were absent, probably because of muscular atrophy. Table 3 shows the percentage

[3] The Boston School prefers the term *long S* rather than *inverted R*.

of upward diphasic and inverted *T* waves obtained in our cases. We note from this table that in our cases the *T* waves were inverted in 26.4 per cent and that the *T* was absent in 33.2 per cent of lead III, whereas in normal cases the *T* was inverted in 30 per cent of lead III.

In tables 4 and 4B the average height and length of *RST* and *P* in millimetres in the three leads are given. Comparing the average values

TABLE 1

Findings of Lewis (52 normal cases) in millimetres

	P	*R*	*S*	*T*
Lead I				
Minimum	Trace	15.0	0	−0.5
Average	0.52	5.16	2.06	1.93
Maximum	1.0	12.0	6.0	5.5
Lead II				
Minimum	Trace	4.0	0	Trace
Average	1.16	10.32	2.23	2.46
Maximum	1.7	16.5	4.5	5.0
Lead III				
Minimum	Trace	2.0	0	−2.0
Average	0.81	6.61	1.73	0.61
Maximum	1.5	14.0	4.0	3.0
Our findings (250 tuberculosis cases)				
Lead I				
Minimum	0	0	0	0
Average	0.41	5.2	2.2	1.4
Maximum	2.0	25.0	15.0	4.0
Lead II				
Minimum	0	1.0	0	0
Average	1.4	10.8	3.8	1.6
Maximum	5.0	33.0	18.0	6.0
Lead III				
Minimum	0	0	0	0
Average	0.94	7.3	1.9	0.40
Maximum	4.0	33.0	17.0	3.0

with those given by Lewis and Gilder in their table of deflections of normal electrocardiograms, obtained from 52 healthy subjects, we note the following: There is very little difference in the average height of the *R* obtained by us as compared with that obtained by Lewis in his table. This is also true of the average height of the *S*, except possibly in the second lead, for which Lewis's figure is 2.23 and ours 3.82. No explana-

tion is forthcoming for this apparent discrepancy nor is it probably significant. When, however, the average height of the *T* obtained by us

TABLE 2

Pardee's schedule

	P	*QRS*	*T*
Height in largest lead	1 to 2 mm.	7 to 16 mm.	1 to 5 mm.
Direction			
Lead I	Upward	Chiefly upward (*R*). *Q* or *S* may be present either singly or together but neither as large as *R*.	Upward
Lead II	Upward	Chiefly upward (*R*). *Q* or *S* may be present singly or together but neither as large as *R*	Upward
Lead III	Upward, diphasic or downward	*Q*, *S* or both may equal but not exceed *RORS*. Group may be of vibratory type	Upward, diphasic or downward
Form	Rounded; may be notched	One, two or three sharply pointed peaks, or vibratory group. A peak may be notched in a lead of relatively small excursion or near base line	Peaked

TABLE 2B

Our schedule of 250 cases à la Pardee

	P	*R* − *S*	*T*
Height in largest lead	0 to 5 mm.	1 to 33 mm.	0 to 6 mm.
Direction			
Lead I	Upward or not visible	*R* upward or inverted	Upward, inverted or not visible
Lead II	Upward or not visible	*R* upward. *S* often present, but not as large as *R*	Upward, diphasic, inverted or not visible
Lead III	Upward or not visible	*R* upward or inverted	Upward, diphasic, inverted or not visible
Form	Rounded or peaked	*R* sharply peaked, notched or vibratory	Rounded or peaked

in our cases is compared to those in Lewis and Gilder's table, we note that our average is lower in all leads. Here a probable explanation may be given. As the summit of the *T* occurs coincidently with the height

of the intraventricular pressure, it would account for the lower values obtained by us as compared with those given by Lewis, since our values were obtained from patients suffering from a chronic disease, in whom an impairment of cardiac muscular tone would be expected, whereas Lewis's values came from healthy individuals. The average height of *P* obtained by us varies but slightly from that given in Lewis's table.

The last table, 5, represents the length of the interval between *T* and *P* in millimetres. This interval corresponds in time with the diastole of the heart. It is not our purpose to enter into a lengthy discussion of the significance of this interval, but we prefer to leave that for a future communication.

The following pictures selected from 250 tuberculous patients appeared instructive from the diagnostic standpoint:

TABLE 3

7 per cent of upward, diphasic and inverted T waves obtained in our cases

We note from this table that in our cases the T waves were inverted in 26.4 per cent and that the T was absent in 33.2 per cent of lead III, whereas in normal cases the T is inverted in 30 per cent of lead III.

250 CASES	UPWARD *T*		DIPHASIC *T*		INVERTED *T*		NO *T*	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Lead I.....	212	84.8			1	0.4	37	14.8
Lead II.....	210	84.0	4	1.6	7	2.8	29	11.6
Lead III.....	83	33.2	18	7.2	66	26.4	83	33.2

	DIPHASIC *T*		INVERTED *T*	
	Cases	Per cent	Cases	Per cent
Leads I and II.....			1	0.4
Leads II and III.....	1	0.4	6	2.4

Figure 8 is an X-ray of an individual of the hypertensive type, with pulmonary tuberculosis involving the right lower lobe, in whom a phrenectomy on the right side was performed. The diaphragm is markedly elevated and pushes the lower part of the lung upward, compressing the lower lobe and changing the axis of the heart somewhat. The electrocardiogram (figure 9) appears to be normal in the first two leads. In the third lead the *T* wave is inverted, as often seen in hypertensive individuals. A moderate tachycardia is also present. A few weeks after the phrenectomy was performed an irregularity of the pulse was noted.

TABLE 4

250 cases

Average height of R in millimetres

Lead I = 5.17
Lead II = 10.78
Lead III = 7.31

Irregular

Lead I: 2 Cases
Lead II: 8 Cases
Lead III: 7 Cases

Average height of S in millimetres

Lead I = 2.15
Lead II = 3.82
Lead III = 1.86

Average height of T in millimetres

Lead I = 1.36
Lead II = 1.59
Lead III = 0.40

Average height of P in millimetres

Lead I = 0.41
Lead II = 1.35
Lead III = 0.94

TABLE 4B

250 Cases

Length of Inverted R

11 per cent in Lead I = 6.88 millimetres

10 per cent in Lead III = 8.48 millimetres

250 Cases

Inverted T

Lead I: 1 case = 0.4 per cent
Lead II: 7 cases = 2.8 per cent

250 Cases

Diphasic T

Lead II: 4 cases = 1.6 per cent
Lead III: 18 cases = 7.2 per cent

The electrocardiogram taken at this time (figure 10) revealed a sinus arrhythmia. According to Lewis, Pardee and others, sinus arrhythmia is attributed to the action of the vagus. The sinoauricular node, the pacemaker of the heart, may be acted upon with a variable intensity by the vagus nerve and the pulse may vary correspondingly. The disturbance of the rhythm results without any change in either the auricular or ventricular complexes. In the slide the distances between the *P*'s, *R*'s and *T*'s of the heart phases are seen to be of unequal length, while the *P*, *R* and *T* remain normal. Sinus arrhythmia is frequently found in young individuals, especially children, and appears to have no clinical

TABLE 5

250 cases: distance between T and P in millimetres

MINIMUM	AVERAGE	MAXIMUM
	Lead I	
0	4.7	13
	Lead II	
0	4.5	12
	Lead III	
0	4.1	11

Average distance

Lead I = 4.78 millimetres
Lead II = 4.46 millimetres
Lead III = 4.1 millimetres

significance. In this particular individual we cannot state whether the sinus arrhythmia was due to the phrenectomy or was merely a coincidence. The arrows in the three leads indicate the changes in the height of the *R* wave. They are higher in full inspiration than in full expiration. We also know from clinical experience that the pulse-rate increases in inspiration and decreases in expiration.

Figure 11 is that of a strong individual, with a cavernous pulmonary tuberculosis on the left, who is being treated by artificial pneumothorax of the left lung. The electrocardiogram (figure 12) is, however, normal, and no evidence of predominance of either ventricle is present, although we expected that the pneumothorax might influence the axis of the heart.

A similar picture is figure 13, of a patient with a partial collapse of the left lung (see arrows) and with a normal electrocardiogram. The T wave in the third lead in this electrocardiogram is inverted, which is physiological in 30 per cent of the cases (figure 14).

Figure 15 is a case of thoracoplasty of the left upper lobe. Here will be noticed a curvature of the spine and an ideal collapse of the upper part of the left lung. The electrocardiogram (figure 16) is typical of a drop heart (low voltage in the first). The heights of R and S are nearly alike in the second and third leads.

Figure 17 is that of a patient with far-advanced tuberculosis, the left lung being involved throughout and the right lung in the upper lobe. There is no enlargement of the right heart seen in the X-ray. The electrocardiogram (figure 18), however, shows a right ventricular predominance, as evidenced by the inverted R_1 and higher upright R_3.

Figure 19 is similar to that of the previous case, but this patient has a drop heart and the electrocardiogram (figure 20) shows a low potential in the first lead. Here also the R_1 is inverted, with a higher R_3, thus indicating a right ventricular predominance (right axis deviation).

In figure 21 we have a patient with caseous pneumonia in the left upper lobe. The picture was taken about twenty-four hours before the patient died. There are present a caseous cavernous tuberculosis in the left lung and some involvement in the right lung. The electrocardiogram (figure 22) shows an inverted T wave in two leads. This is regarded as of grave prognostic import in an article published recently from the Mayo Clinic and quoted by Pardee.

An inverted T_2 and T_3 is less seriously regarded than an inverted T_1 and T_2. The cause of this abnormality is not satisfactorily explained. In fact, there is no agreement among students of the electrocardiograph as to exactly how the T wave is produced. It is a well-known fact that digitalis and morphine may frequently produce an inverted T in two or more leads. Pardee believes that an inverted T indicates diffuse myocardial disease when no other apparent cause for muscular intoxication can be found. Lewis, on the other hand, has found persistent inverted T waves in some individuals without any impairment of health for years.

Figure 23 is an X-ray of a far-advanced case of cavernous tuberculosis. The electrocardiogram (figure 24) was taken while the patient was in an extremely toxic condition. It shows an inverted R_1 and an inverted T_3, and a tachycardia. The arrows in leads II and III indicate the apices

of the *R* and *S* waves, the variation being due to the respiration, as was demonstrated in the case of sinus arrhythmia.

Figure 25 is an X-ray of a patient with an artificially collapsed left lung (see arrows). There is fluid in the left costophrenic angle. The heart is extremely narrow and the electrocardiogram (figure 26) is typical of a drop heart (low voltage in the first and third leads, direction of the waves normal).

Figure 27 is that of another drop-heart case, with a far-advanced cavernous tuberculosis in both lungs (see arrow). The cavities are not seen very clearly, as is usual in teleoroentgenographic heart pictures taken at a seven-foot distance. The electrocardiogram (figure 28) shows a low voltage in the first lead with an inverted *R* wave. One sees also an irregularity, which is especially noticeable in the second and third leads. The arrow in lead III points to the *T* and *P* waves, which nearly coincide with each other. We consider this irregularity as due to severe myocardial changes. The clinical pictures speak for an unfavorable prognosis.

The next picture, figure 29, represents a case of ideal thoracoplasty in a young woman with a drop heart. The first lead of the electrocardiogram (figure 30), with its low voltage, confirms our clinical diagnosis of drop heart.

The explanation for figure 31 is extremely difficult. It represents a case of far-advanced pulmonary tuberculosis of the left lung, in which only a small amount of air had been given previous to the patient's admission to our hospital. The electrocardiogram (figure 32) shows an inverted R_1 and a higher upright R_3, which is probably due to pulmonary involvement and the burden on the right heart. After the second gas filling, given in our hospital, an ideal collapse resulted (figure 33, see arrow) but the electrocardiogram (figure 34) suddenly changed. The inverted R_1 became normal and the inverted T_3 changed into a diphasic *T*. There are two explanations for this sudden change. In the first place, the compression of the lung might have caused a release of the pressure of the pulmonary capillaries, and therefore placed less burden on the right heart and changed the right ventricular predominance into a physiological condition. The other explanation may be that the air caused pressure on the overburdened right ventricle, thus giving the left ventricle a preponderance over the right one. Considering the topography of the two ventricles in the chest, as given in an excellent X-ray sketch by Brown and Weiss (6) (figure 35), there will be noticed

that the right ventricle is situated anteriorly in the left side of the chest. The left ventricle is nearer the posterior mediastinum. A predominance of either ventricle cannot be expected in a pneumothorax case, in which there are no pleural or pericardial adhesions present in front or in back of the heart, since the air presses on both ventricles alike. A right ventricular predominance, therefore, may be expected only in those left-sided pneumothorax cases in which the adhesions are in front, and a left ventricular predominance only when the adhesions are posterior.[4]

Figure 36 is a case of latent pulmonary tuberculosis with a peculiar cardiac form. The arrow shows the prominent arch of the pulmonary artery, the heart is enlarged *in toto*, especially to the right, and the right hilum shadow represented by the right branch of the pulmonary artery (see arrow 2) is larger than normal. Our clinical diagnosis of this case was patency of *ductus arteriosus botalli*. The electrocardiogram (figure 37) shows a right ventricular predominance, inverted R_1 and high upright R_3. The picture is otherwise normal.

Figure 38 is an X-ray of a patient suffering from cavernous pulmonary tuberculosis and a chronic gonorrhoea. The clinical cardiac findings were negative except that from time to time the patient showed an extremely low pulse (48 to 60 per minute). The pulse-rate taken in the

[4] Dr. Hubert Mann, New York, with whom one of us communicated personally about the case shown in figure 31, expresses his opinion as follows:

"Changes in the electrocardiogram due to pneumothorax are due not so much to changes in the situation of the heart as to changes in the direction of the cardiac axis. We, therefore, have the following possibilities:

"(1) The cardiac axis may be approximately unchanged, due either to the retention of the heart in its usual position by adhesions or to the symmetrical displacement of all parts of the heart. In this case the electrocardiogram will be approximately unchanged by the pneumothorax.

"(2) The cardiac axis may become more vertical due to the fact that the cardiac apex is relatively more displaced than the base. In this case the electrocardiogram will approach the type known as right ventricular predominance, i.e. R_1 inverted.

"(3) The cardiac axis may become more horizontal due to a relatively greater displacement of the base and a fixation of the apex by adhesions or by the natural ligaments. In this case the electrocardiogram will approach the type known as left ventricular predominance, i.e., R_3 inverted.

"Apparently the electrocardiogram of case number 31 illustrates the third possibility. The X-ray examination will give added confirmation as to the relative displacement of the cardiac base and apex and the consequent alteration of the cardiac axis. The changes in the T wave are subject to considerable variation because of the fact that displacement of the heart is almost always accompanied by some rotation, a factor which seems to be very potent in altering the shape and direction of the T wave. The effect of this combination of alteration of cardiac axis and rotation of the heart is too complicated to permit of satisfactory analysis or prediction."

electrocardiogram was 60. Besides the inverted R_1 and the upright R_3 (right ventricular predominance), it was noticed that the *QRS* distance was longer than normal. According to Lewis, the greatest distance between *Q* and *S* should not exceed 2 to 2½ squares, which means 0.10 inch. In our case (figure 39) the distance was 3 squares, equaling 0.12 inch, and an abnormal notching of the *R* group is seen. This is very frequently a symptom of delay in conduction caused by bundle-branch block.

Figure 40 is an X-ray of a child of tuberculous parentage, admitted to the hospital preventorium as a contact case, without any symptoms of active pulmonary tuberculosis. The heart of this child is normal in shape. In an examination of hundreds of X-ray pictures of children, we have not discovered a case of typical drop heart. The drop heart appears to develop only after the characteristics of the body frame have manifested themselves, and, as we have already stated, the shape of the body frame influences the axis of the heart. This may account for the fact that we so rarely see the drop heart in young children. From the anthropological studies of Martin, Kretschmer and others, we find that the slender, tall "leptosome" type of Kretschmer is characterized by rapid growth in height after puberty. Apparently, however, the electrocardiogram in these asthenic types frequently shows this tendency before it is apparent in the body frame. The electrocardiogram (figure 41) shows an extremely low potential in lead III, which, we have already stated, appears to be characteristic of drop heart. The electrocardiographic curves in children frequently show a low potential, but in all three leads, whereas in this case it is present in lead III only.

SUMMARY AND CONCLUSIONS

1. The electrocardiogram seems to be of great value in pulmonary tuberculosis, giving information in regard to the heart not otherwise obtainable with the same accuracy.

2. The low potential sometimes found in lead I or III, especially the former, points to the presence of drop heart or *cor pendulum*.

3. The average value in height of the *T* wave was found to be lower than that given by Lewis in his chart of 52 normal individuals, which would indicate that there exists in tuberculous individuals a weakened cardiac musculature, a condition long suspected by clinicians, but not proved except upon autopsy.

4. The diagnosis of cardic lesions combined with pulmonary tuberculosis is simplified by the use of the electrocardiograph.

5. Collapse treatment does not always influence the electrocardiographic picture.

6. A right ventricular predominance (right axis deviation) was present in 10 per cent of the 250 cases studied. A left ventricular predominance was also present in 10 per cent of these cases. An inverted *T* wave in two leads was seen only in cases in which the prognosis was doubtful or unfavorable.

We wish to express our thanks to Dr. L. T. Black, Mr. Max Kramer and Miss Rubye Willens for their help and assistance in the preparation of this paper.

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Plate 1

FIG. 1. Normal electrocardiogram. *P* wave = auricular complex. *QRST* = ventricular complex. *QRS* precedes ventricular contraction. *T* coincides with height of ventricular contraction.

FIG. 2. X-ray of heart in an asthenic type of individual. Far-advanced pulmonary tuberculosis. Drop heart.

FIG. 3. Same case as figure 2. Low potential in first lead.

FIG. 4. Hypersthenic type of individual. Tuberculous infiltration of right apex. Aortitis. Heart enlarged to the left and resting on the diaphragm.

FIG. 5. Same case as figure 4. Left ventricular predominance (inverted R_3, greater in size than upright R_1).

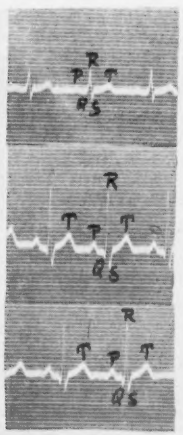
FIG. 6. Far-advanced pulmonary tuberculosis, with cavity in left upper lobe, marked fibrotic cirrhosis of left lung, and pleural adhesions pulling the heart and mediastinum to left.

FIG. 7. Same case as figure 6. Slight right ventricular predominance (inverted R_1, height of R_3 exceeding that of R_1).

FIG. 8. Hypertension type after phrenectomy on the right. Diaphragm elevated, pushing the involved lower right lung upward.

FIG. 9. Same case as figure 8. Normal electrocardiogram in the first two leads. Third lead shows an inverted *T* wave.

FIG. 10. Same case as figure 8. Sinus arrhythmia after phrenectomy. Distance between the *P*'s, *R*'s and *T*'s of the heart phases of unequal length. *P*, *R* and *T* normal.



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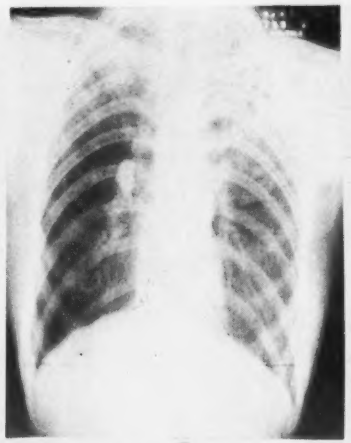

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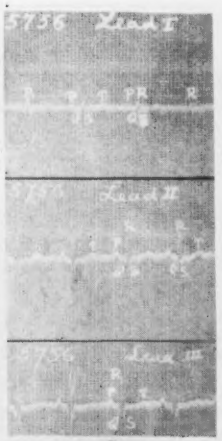

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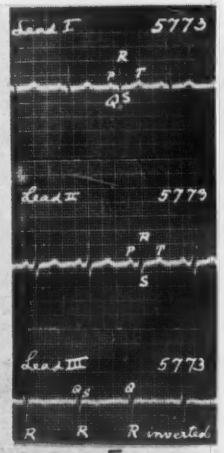

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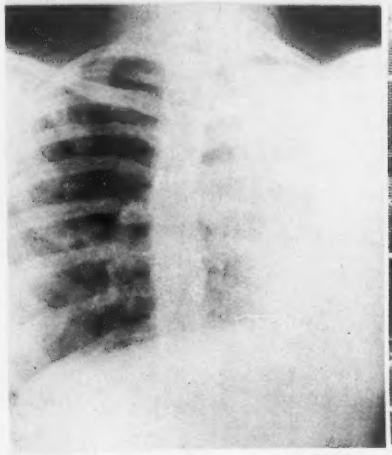

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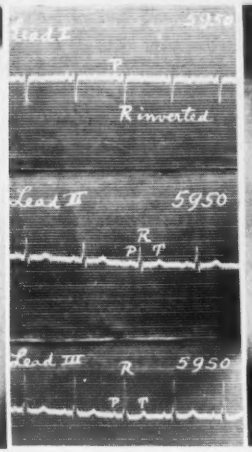

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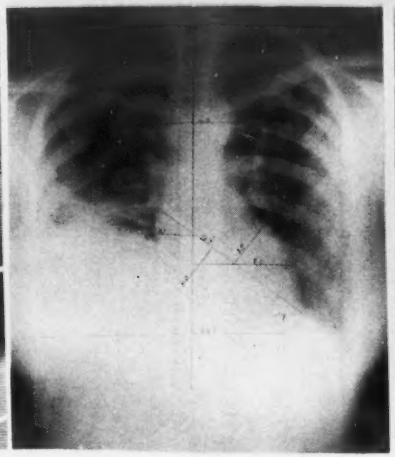

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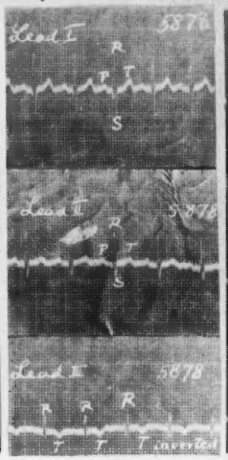

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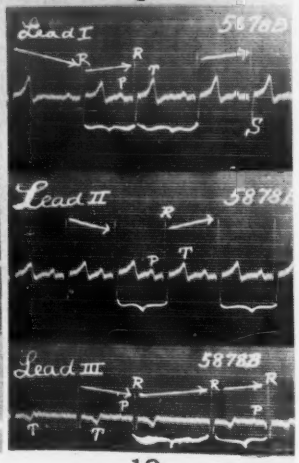

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PLATE 1

Plate 2

FIG. 11. Collapse of cavernous left lung.

FIG. 12. Same case as figure 11. Electrocardiogram normal.

FIG. 13. Collapse of the left lung.

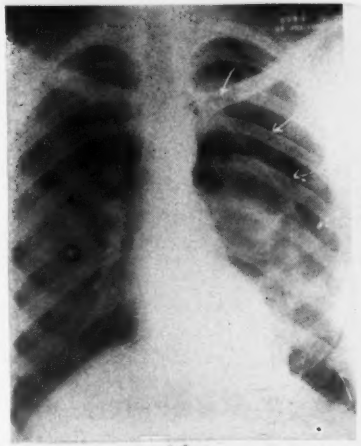
FIG. 14. Same case as figure 13. Electrocardiogram normal. T_3 inverted (physiological in 30 per cent of the cases).

FIG. 15. Thoracoplasty of left upper lobe. Curvature of the spine following thoracoplasty.

FIG. 16. Same case as figure 15. Electrocardiogram characteristic for drop heart (low voltage in lead I; height of R and S nearly alike in lead II and III).

FIG. 17. Far-advanced pulmonary tuberculosis, with involvement of left lung and upper right. No enlargement of the right heart seen in the X-ray.

FIG. 18. Same case as figure 17. Right ventricular predominance (inverted R_1 and higher upright R_3).



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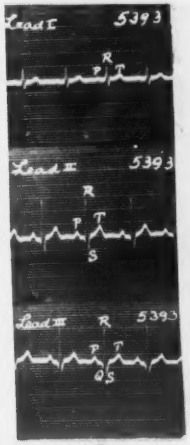

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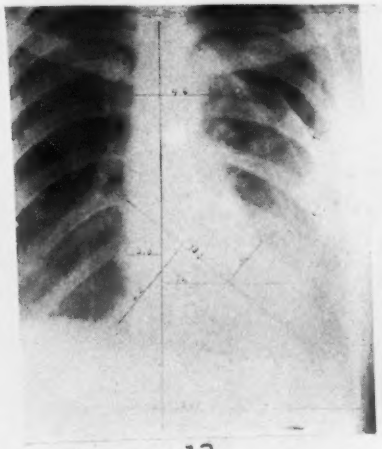

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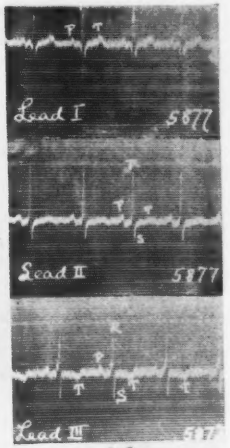

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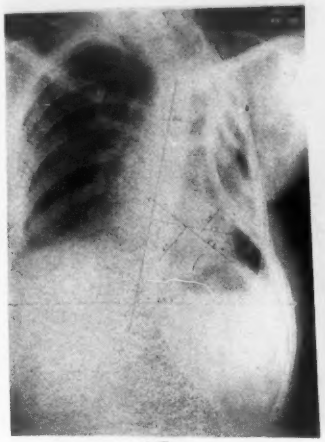

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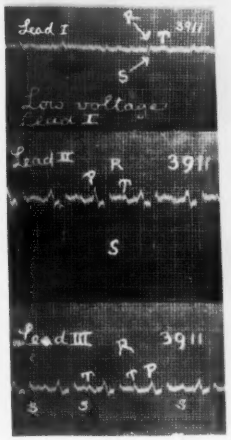

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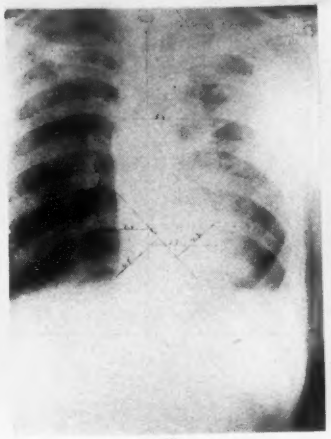

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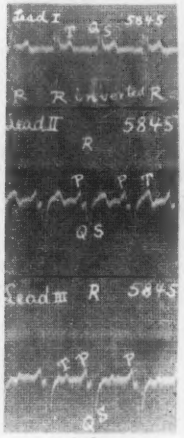

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PLATE 2

Plate 3

FIG. 19. Similar case to that of figure 17. Drop heart.

FIG. 20. Same case as figure 19. Electrocardiogram characteristic for drop heart. R_1 inverted; right ventricular predominance.

FIG. 21. Caseous pneumonia of left upper lobe. Picture taken 24 hours before death.

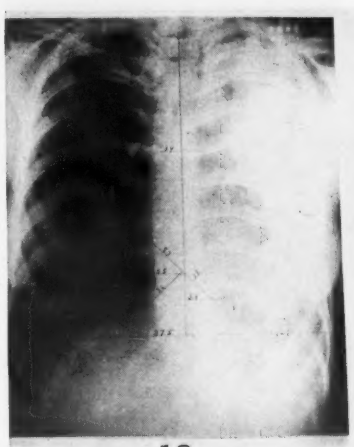
FIG. 22. Same case as figure 21. T inverted in two leads (grave prognostic sign).

FIG. 23. Far-advanced cavernous tuberculosis of left lung.

FIG. 24. Same case as figure 23. Electrocardiogram shows inverted R_1, inverted T_3 and tachycardia. Arrows in leads II and III indicate heights of R and S waves, the variation being due to respiration as seen in figure 10.

FIG. 25. Collapse of left lung. Fluid in left costophrenic angle. Drop heart.

FIG. 26. Same case as figure 25. Electrocardiogram characteristic for drop heart.



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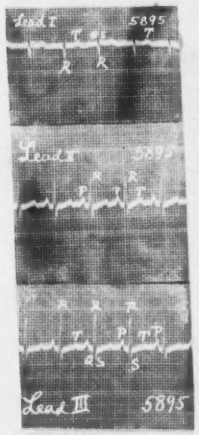

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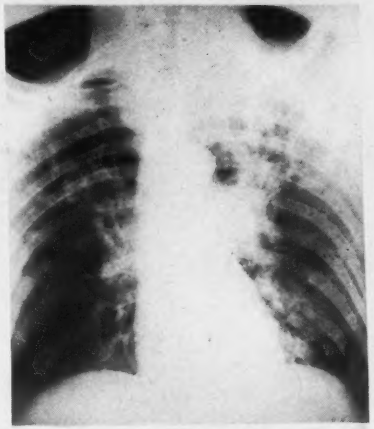

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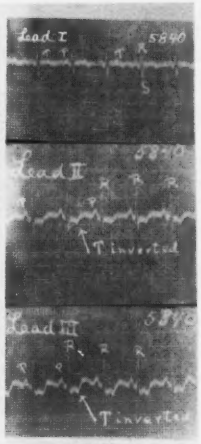

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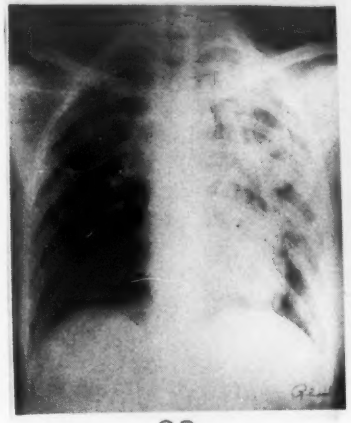

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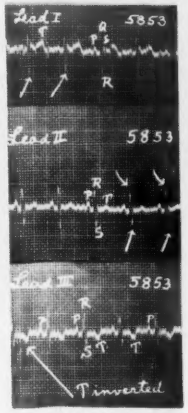

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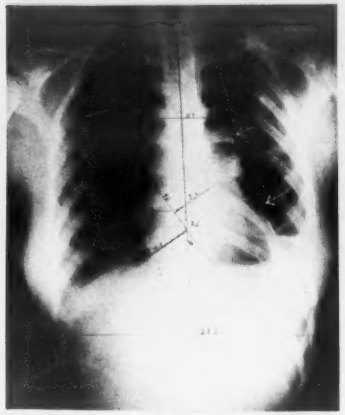

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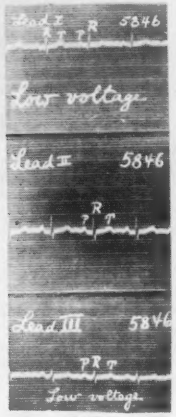

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PLATE 3

Plate 4

FIG. 27. Far-advanced cavernous tuberculosis in both lungs (see arrows). Drop heart. Cavities not seen very clearly, as is usual in teleoroentgenographic pictures.

FIG. 28. Same case as figure 27. Low voltage in the first lead (drop heart). R_1 inverted. Irregularity especially noticeable in second and third leads. Arrow in lead III points to the P and T waves, which nearly coincide with each other, due to severe myocardial changes. Prognosis unfavorable.

FIG. 29. Ideal thoracoplasty in young woman with drop heart.

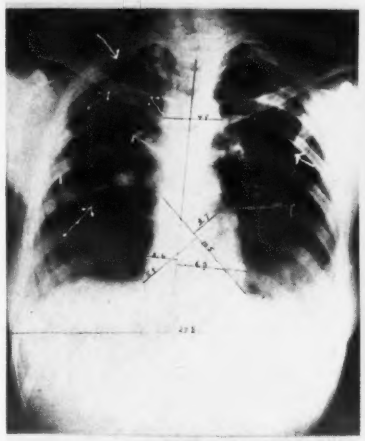
FIG. 30. Same case as figure 29. Electrocardiogram characteristic for drop heart. Low voltage in first lead.

FIG. 31. Far-advanced pulmonary tuberculosis of the left lung (small amount of air given previous to patient's admission to hospital).

FIG. 32. Same case as figure 31. R_1 inverted, R_3 upright and higher. Right predominance.

FIG. 33. Same case as figure 31. After further gas-filling. Collapse ideal.

FIG. 34. Same case as figure 33. Electrocardiogram differs from figure 32 (inverted R_1 becomes normal; inverted T_3 changes into a diphasic T_3).



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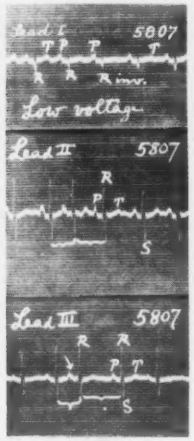

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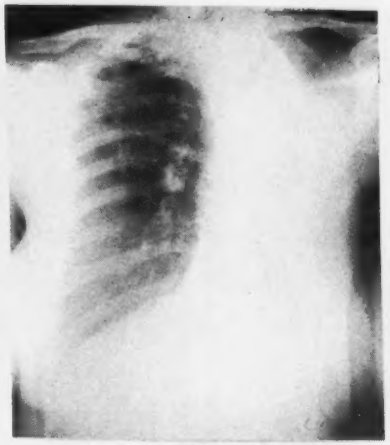

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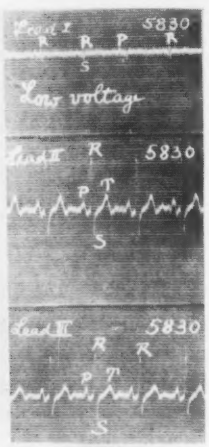

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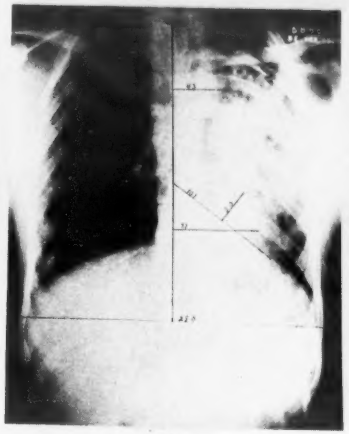

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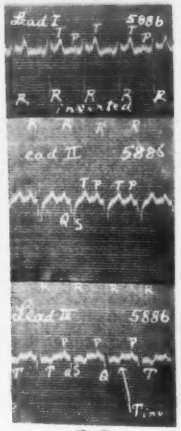

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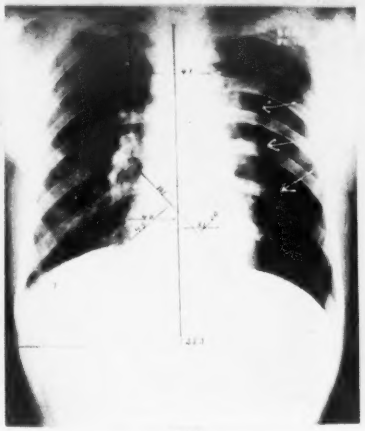

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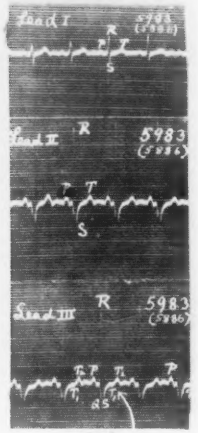

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PLATE 4

Plate 5

FIG. 35. X-ray sketch (Brown and Weiss: Lateral views of the heart and aorta, Jour. Amer. Med. Assoc., January 22, 1927, lxxxviii, 226). Right ventricle anteriorly situated, left ventricle posteriorly.

FIG. 36. Latent pulmonary tuberculosis. Patency of *ductus arteriosus Botalli*. Arch of pulmonary artery prominent (see arrow). Heart enlarged *in toto*, especially to the right. Right hilum shadow represented by right branch of pulmonary artery (see arrow 2); larger than normally.

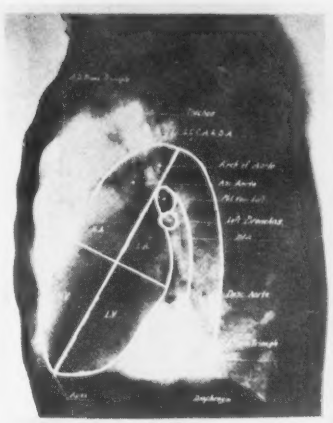
FIG. 37. Same case as figure 36. Right ventricular predominance (R_1 inverted; R_3 higher and upright).

FIG. 38. Case of far-advanced pulmonary tuberculosis complicated by chronic gonorrhoea. Clinical heart findings showed extremely low pulse (48 to 60 per minute).

FIG. 39. Same case as figure 38. Electrocardiogram shows inverted R_1 and upright R_3. Right ventricular predominance. QS distance longer than normal (3 squares = 0.12). Delayed conduction caused by bundle-branch block.

FIG. 40. X-ray of child of tuberculous parentage. Heart normal.

FIG. 41. Electrocardiogram shows low potential in lead III, which is characteristic for drop heart. Electrocardiographic findings seem to precede the constitutional change of the body frame, as seen in drop-heart cases after puberty.



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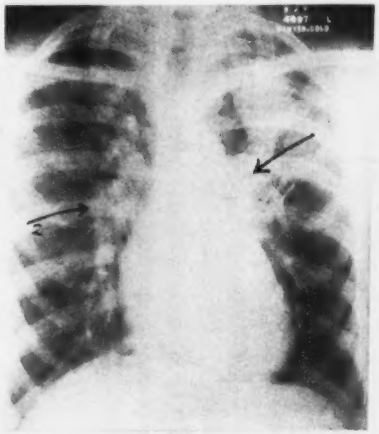

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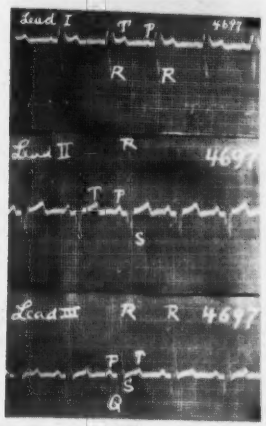

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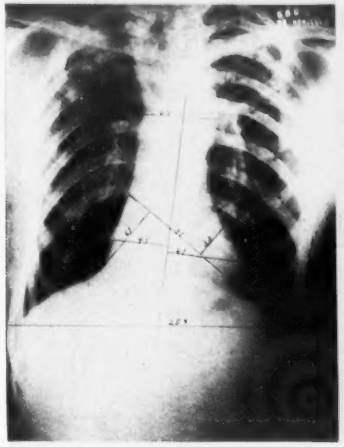

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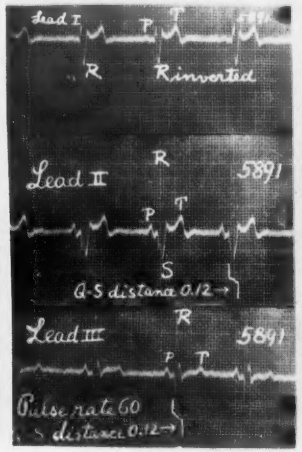

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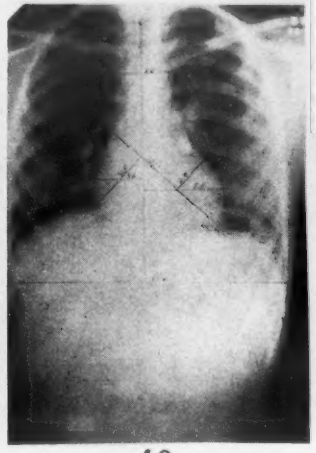

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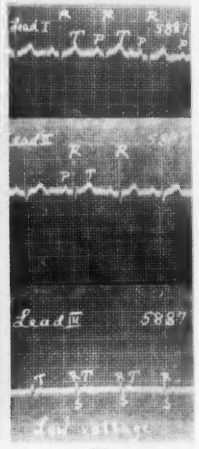

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PLATE 5

HERNIA OF THE LUNG

With Report of a Spontaneous Case

F. JANNEY SMITH AND BEN. I. JOHNSTONE[1]

By the term *hernia* is meant the protrusion of some viscus from its normal situation, through an opening in the walls of the cavity within which it is normally contained. True hernia of the lung is relatively rare, and many clinicians of experience have not had the opportunity of observing the condition. Roland, in 1499, is given credit for describing the first case, and up to 1800, only about 15 cases were reported. Montgomery and Lutz, in a recent extensive review of the literature, were able to collect only 165 cases.

Case Report

Case no. 88,923: Male, age 48, American, banker, was admitted February 14, 1927, complaining of cough and a lump in the left chest. About sixteen months previously he had developed a nonproductive cough, which, after persisting for about five months, had disappeared. Five months before admission the cough had returned and gradually grown worse. He began to lose strength and weight. Two days before admission he first noticed fever and night-sweats. At no time was he compelled to stop work. There was no history of haemoptysis, pleurisy, or exposure to tuberculosis.

Shortly after the first onset of cough he noticed a lump about the size of a bean in the region of the left nipple. It was painless, appeared only on coughing, and did not enlarge until about two weeks before admission, when after a severe coughing spell he noticed that the small lump had suddenly become a distinct bulging. It appeared only with cough or forced expiration, and, as far as the patient could remember, there had been no particular pain associated with its initial appearance. Each time it appeared he noticed a distinct gurgle, and there was slight tenderness over the tumor. The past history was negative for injury or operation on the chest-wall, and the patient had had no other hernia. He denied venereal disease by name and symptoms.

The patient, a short, rather poorly nourished adult white male, had a distressing but only slightly productive cough. Height 5 ft., 5 in., weight 126 lbs., temperature 101°, pulse 96, and respirations 30. The teeth showed con-

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siderable pyorrhoea, and a number of them were devitalized. The heart and mediastinum were displaced a little to the left; otherwise a detailed physical examination disclosed no remarkable pathological changes except in the respiratory system. The trachea was displaced to the left, and the left upper front of the chest showed retraction. The whole left side moved less than the right. On the right, the lung base was at its normal level and moved satisfactorily with respiration. There was impaired resonance to percussion in the interscapular area. The breath-sounds here were bronchovesicular, while in the second and third interspaces anteriorly they were definitely bronchial, and showers of medium moist râles were heard at the end of inspiration and after cough. No râles were heard posteriorly. On the left, the lung base was 2 cm. higher than on the right, and did not move with respiration. The percussion note was impaired over the whole of the left chest, and showers of medium moist râles, at the end of inspiration and after cough, were heard all over the left back and front, being especially marked at the level of the third and fourth interspaces anteriorly.

On the chest, so that the left nipple occupied almost a central position, was a localized bulging, which appeared on coughing, and partially disappeared spontaneously, on cessation of the cough. When fully expanded, this prominence measured 8.5 cm. horizontally and 5.5 cm. vertically, the inner border being 6 cm. to the left of the midline in the fourth interspace, and the outer border reaching the anterior axillary line. The portion that did not spontaneously disappear crepitated markedly, and could be readily reduced by manipulation, through a depression in the fourth interspace, over which, if a finger was firmly held, the bulging was prevented from appearing, even on hard coughing. When the left pectoral muscles were voluntarily made tense, the bulging, instead of appearing as described above, appeared largely from beneath the lateral border of the left pectoralis major muscle. Percussion over the tumor yielded a peculiar tympanitic note. Each time the bulging occurred it was accompanied by a squeaking sound. The breath-sounds over the tumor were extremely loud, and there were many harsh popping sounds on inspiration and expiration.

Figure 1 is a photograph of the chest-wall with the hernia completely reduced, while *figure 2* is a photograph taken a few seconds later from the same position, showing the hernial protrusion on forced expiration.

Figure 3 represents one of the stereoscopic plates of the chest. These showed the heart to be about normal in size, but pulled somewhat to the left. There was a marked increase in density over the lower three-fourths of the left lung field, with some elevation of the diaphragm along the lateral wall. There was also a definite increase in density in the left apex, which, however, did not appear to be definitely parenchymatous. On the right, in the lower part of the upper lobe, spreading out in a fan-shaped form from the root of the lung, there was an area of markedly irregular increase in density. The tumor

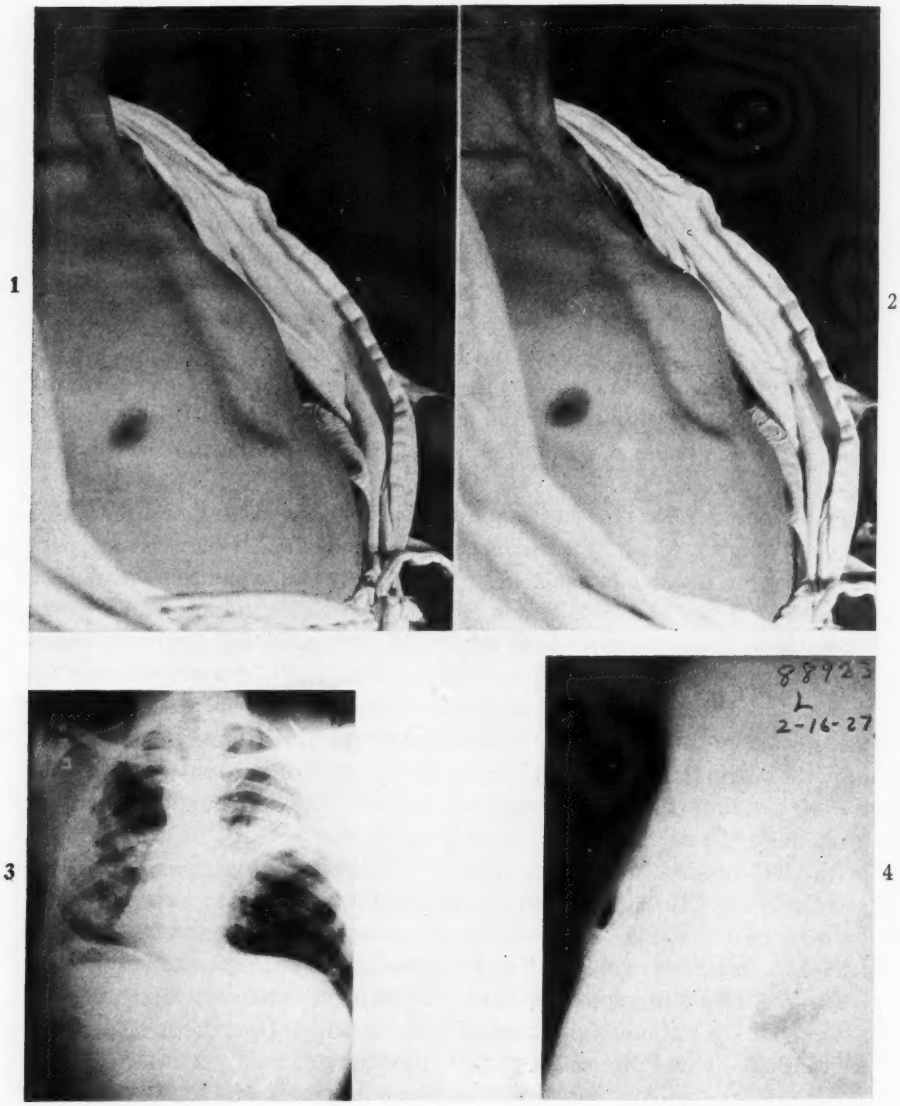

FIG. 1. CHEST-WALL WITH THE HERNIA COMPLETELY REDUCED

FIG. 2. CHEST-WALL SHOWING THE HERNIAL PROTRUSION ON FORCED EXPIRATION

FIG. 3. STEREOSCOPIC X-RAY OF THE CHEST

FIG. 4. OBLIQUE X-RAY OF THE CHEST TAKEN WHILE THE INTRATHORACIC PRESSURE WAS INCREASED BY FORCED EXPIRATION

area described clinically could not be seen. These changes had the configuration of tuberculosis, but not the typical distribution.

Figure 4 represents an oblique plate of the chest, taken while the intrathoracic pressure was increased by forced expiration. This shows, beneath the left pectoralis major muscle, an area of decreased density lying outside the thoracic cavity, which represents a bubble of air.

Fluoroscopic examination confirmed the above findings, and showed a large bubble of air outside the thoracic cavity, which increased or decreased as the intrapulmonary pressure was increased or decreased. This bubble was seen to communicate with the air-containing lung tissue within the thoracic cavity.

Examination of the sputum showed many tubercle bacilli. The blood-Wassermann was strongly positive on two occasions. Examination of the spinal fluid was reported as follows: Initial pressure 12 mm. Hg., cells 2, globulin faint trace, Wassermann negative, Lange 4420000000, Mastic 5544310000. The urine, blood counts, and blood chemistry, were not abnormal.

The patient was seen to be suffering from active, bilateral, chronic, ulcerative, pulmonary tuberculosis, and also syphilis, as evidenced by the positive blood-Wassermann. The tumor on the chest was a spontaneous pneumonocele, which developed secondary to the chronic cough. It is to be noted that it appeared at the site of a normal *locus minoris resistentiae*, in the fourth interspace, anteriorly, near the costochondral junction.

Throughout his stay in the hospital the temperature was remittent, varying during the first week from 99° to 102°, during the second from 98.6° to 101°, and during the third week from 98.6° to 100°.

Because of the febrile course, and the associated pathological conditions, surgery did not seem indicated at the time of hospitalization. The hernial opening was protected by a piece of firm felt, strapped tightly to the chest by wide strips of adhesive, which extended almost completely around the chest. The patient was discharged, three weeks after admission, to a sanatorium.

DISCUSSION

In normal inspiration and expiration the lungs merely follow the movements of the chest-wall, without any tendency to hernial protrusion. In forced expiration, however, as in coughing, blowing wind instruments, and lifting, the intrathoracic pressure is considerably raised. Such increased pressure may act on a normal chest-wall, or against one weakened by congenital defects or trauma. A weakened area, whether it be due to an anatomical peculiarity, trauma or congenital defect, represents a *locus minoris resistentiae.*

If the wall is normal, herniation rarely occurs, and then only if the force is excessive or oft-repeated over a long period of time. When it

does take place through a normal thorax, it is liable to occur in certain definite areas, inasmuch as the chest-wall is so developed that it yields to the same force in different places with varying degrees of facility. The superior aperture of the thorax is one of these areas of lessened resistance, though herniation here is relatively rare. The chief structure limiting the excursion of the apex is the dome of the pleura, fortified by the deep cervical fascia and the overlying neck muscles. The interval between the scalenus anticus and the sternomastoid is the weakest place, and the usual site of herniation in this locality. Anteriorly, in the interspaces near the sternum, and posteriorly, near the vertebrae, weakened areas also normally occur. This is due to the fact that the external group of intercostal muscles extends forward only as far as the costochondral junction, and behind the internal group extends only to the angle of the ribs. The intercostal muscles are represented in these areas by fibrous sheaths. Most commonly herniation occurs anteriorly, because this *locus minoris resistentiae* is protected by the pectoral muscles alone, and they do not afford the support given posteriorly by the trapezius, latissimus dorsi and rhomboidei.

Congenital defects are usually located near the sternum, but they may occur in the superior aperture, diaphragm, ribs, or musculature. Trauma may occur in any locality.

According to its location, the hernia may be cervical, thoracic or diaphragmatic. The cervical group is relatively rare, the thoracic most common, and only one case of diaphragmatic lung hernia has been reported. This was Beale's case, which followed an injury to the diaphragm, in which the intestine was perforated. The patient died of general peritonitis, and at autopsy pulmonary tissue was found in a subphrenic abscess, but no opening could be made out in the diaphragm. The rare occurrence of diaphragmatic hernia of the lung is due to the existence of positive intraäbdominal and negative intrathoracic pressures.

Herniae of the lung vary greatly in size, from that of a small egg to that of an orange or larger. They may be single, multiple, unilateral or bilateral, and may or may not be enclosed in a pleural sac.

In an analysis of 61 cases, Montgomery and Lutz reported 21 as occurring under fifteen years, 19 between fifteen and forty-five years, and 21 over forty-five years. They are much more common in men than in women, due to the fact that the male sex is more exposed to trauma and lives more strenuously.

Hernia of the lung may be classified as *congenital* or *acquired*, and the latter group may be either *traumatic* or *spontaneous*. From a study of 85 cases, Auler and Urbach reported the relative frequency of the various forms as congenital 24, traumatic 47, and spontaneous 31 per cent. Montgomery and Lutz, from 165 cases, estimated the relative frequency as congential 18, traumatic 50, and spontaneous 32 per cent, figures which correspond closely with those of Auler and Urbach. From a series of 78 cases, Montgomery and Lutz reported their location as follows: cervical 16, of which 10 were on the right and 6 on the left side; anterior chest-wall 57, thirty-four being on the right and 23 on the left; while only 5 were found on the posterior chest-wall, of which 3 were on the right and 2 on the left. From this series it is seen that they are somewhat more common on the right than on the left side.

Congenital Lung Hernia: Congenital pneumonocele is secondary to sternal clefts or deficiencies elsewhere in the thorax. These result from arrested growth of the structures composing the chest-wall. These defects are covered by fibrous tissue, as a rule, and result from various intrauterine abnormalities, such as amniotic bands, pressure of the elbow of the foetus against the chest-wall, lack of amniotic fluid, or pressure from uterine fibroids. As the lungs are in a state of collapse during uterine life, there is often no evidence of trouble until some time after birth. It may be months, or even years, before the hernia appears, and, because of this, confusion may arise as to its congenital origin. On the other hand, a traumatic hernia may occur early in life, and simulate a congenital hernia. Hochsinger claims that all lung herniae occurring in the first few weeks of life must be considered as congenital.

Traumatic Lung Hernia: These herniae are secondary to injury to the chest-wall, and herniation may occur immediately or may not develop until later, when bulging occurs at the site of the scar. Morel-Lavallee gave the name *consecutive* to such herniae occurring late after the trauma, but most writers have tended to disregard this term and include all under traumatic hernia. Trauma may result from a variety of causes. One case is reported of a lung hernia, which developed at the site of repeated thoracenteses, after the scar had gradually thinned and stretched. Injuries from bullet and bayonet wounds in battle are particularly common. However, herniation is rare, compared with the number of penetrating wounds of the chest-wall. During the American Civil War only 3 cases were reported, and during the Russo-Japanese War only 5 cases occurred among at least 20,000 wounds of the chest. No reported cases could be

found as having occurred in the late war. They are more frequent following stab and bayonet wounds than after bullet wounds, because of the small entrance and exit in the latter case. The rarity of protrusion of the lungs in such cases is due to the inherent elasticity of the lung, which causes it to contract and retract from the chest-wall, when the intrapleural and intrapulmonic pressures become equal. Herniation, if it does occur, is often complicated by haemothorax and pneumothorax. Many writers prefer the term *traumatic evisceration* to that of hernia in those cases in which a protrusion occurs as the result of a penetrating wound. Traumatic hernia may occur without an external injury. Squeezes, falls from a height, or nonunion of fractured ribs, may result in a *locus minoris resistentiae*, and herniation subsequently occur.

Spontaneous Lung Hernia: In such cases there is no congenital or traumatic defect in the chest-wall, but long-continued or excessive increased intrathoracic pressure and strain force a portion of the lung through an area in the chest-wall which is relatively weak, due to its anatomical peculiarity, as described above.

The hernia, in a number of cases, is directly due to cough secondary to such pathological conditions as chronic bronchitis, tuberculosis or whooping cough. The increased pressure may result from the blowing of wind instruments, the lifting of heavy weights, or parturition.

In a study of 26 cases of spontaneous pneumonocele Urbach found the following distribution: supraclavicular 7, first interspace 6, second interspace 2, fourth interspace 1, fifth interspace 2, sixth interspace 3, seventh interspace 2, eighth interspace 1, and sternum 1.

Certain authors claim that hernia may result from disease of the thoracic boundaries, such as carious ribs, empyema necessitatis, perforating lung abscess, or malignant growths. Such conditions may so destroy the chest-wall that nothing is left but the skin and subcutaneous tissues. Over such an area there may be a distinct bulging on expiration and coughing, which may have the appearance of a hernia but lacks the characteristic crepitation.

SYMPTOMS AND SIGNS

These will vary according to the type of hernia present. As a rule, especially in nontraumatic hernia, there are very few symptoms. In some, during the initial period of development, there may be pain. Tenderness over the area frequently persists. Other patients may not be

conscious of anything wrong until an abnormal tumor is noticed on the chest-wall. Sometimes, as in the case reported above, a distinct sound may be associated with the appearance of the hernia. Occasionally there is a chronic spasmodic nonproductive cough, secondary to the hernia, which disappears when the hernia is cured. In the acute traumatic variety, the picture is obscured by the severe symptoms secondary to injury of the chest-wall, pleura or viscera. Rarely a pneumomocele becomes strangulated, and local inflammation, either acute or chronic, may be present at the site of the hernia.

On inspection a mass is visible upon the chest-wall, which appears when the intrapulmonary pressure is increased. This tumor comes through an orifice in the parietes, and may reduce itself, partially or completely, with decrease of the intrathoracic pressure. The protruding mass is usually ovoid. There may be associated a local scar, or a bony irregularity, or signs of inflammation. On palpation the tumor is found to consist of a round crepitant mass. Tactile fremitus is increased. It is frequently possible to grasp the lung, and hold its border during respiration. The hernial orifice is usually easily palpated, and may be bony or fibromuscular. Frequently the tips of one or more fingers can be inserted into the orifice, and in this way the hernia prevented from appearing. The percussion note is resonant and tympanitic, with probable variation between abdominal and chest resonance. The auscultatory findings depend on the pathological changes present. Vesicular, whistling and crepitant râles may be heard, and fremitus is usually increased.

DIAGNOSIS

This should not occasion any great difficulty. A careful history, a thorough examination of the entire thorax, and the recollection that a lung hernia, as a rule, presents a smooth soft elastic crepitant swelling, that is resonant to percussion and usually reducible, partly or completely, through a palpable orifice, will prevent diagnostic errors. Various authors have called attention to the need of differentiating hernia from various other tumors of the chest-wall, such as localized subcutaneous emphysema, perforating empyema or lung abscess, aneurysm, fibroma, lipoma, angioma, sarcoma, cysts, dilated veins, and abdominal *hernia intercostalis*. Merely to mention is to differentiate the majority of the above tumors.

TREATMENT

In a few instances lung herniae are reported to have cured themselves. Such cases have become strangulated, and the hernial orifice subsequently closed spontaneously. Wightman reports a case in which this occurred. The majority, however, persist, and in these cases the treatment may be either medical or surgical. The decision in any one case will depend upon the type of hernia, the condition and occupation of the patient, and the associated pathological changes. Certain herniae persist because the chronic cough which caused them continues. In these cases the clearing up of the bronchitis or cause of the cough will prevent the recurrence of the hernia. When the etiology is occupational, as in laborers doing heavy lifting, glass-blowers, or players of wind instruments, changing the type of work may be all that is necessary. If this is not feasible the hernial opening may be supported by a variety of contrivances, their nature depending upon the ingenuity of the observer. Elastic bands, corsets, and obturators of various kinds strapped to the chest-wall have been used. These frequently relieve symptoms and prevent the hernia from growing larger. A few cases have been reported in which with such treatment the opening closed spontaneously.

If the hernia produces much inconvenience and the general condition of the patient warrants it, surgical measures may be advisable. The early writers were not in favor of operative interference, although as early as 1898 plastic operations of various kinds were described. Periosteum, bone-flaps from the sternum, or strips of rib were used to close the orifice. Tuffier reports a case in which he ligated the hernial sac. This was followed by a cure. Graham attempted to support the orifice in his case by muscle, and, failing in this, finally packed the wound with iodoform gauze. The resulting inflammatory reaction formed sufficient scar-tissue to produce a cure. Montgomery and Lutz report a case cured by a plastic operation, in which the adjoining ribs were split and sutured over the orifice.

Because of the rarity of the condition the individual experience of any one observer is very limited; hence the relative value of different procedures has not been established. No one method of treatment will apply to the various types of hernia, and the therapy adopted must be decided on the merits of the individual case.

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THE FATE OF HUMAN AND AVIAN TUBERCLE BACILLI IN THE LIVER OF BIRDS

JOHN C. ROGERS[1]

In 1914 Kyes (1) demonstrated that certain vascular endothelium performs a definite normal physiological phagocytic function in destroying an animal's own red blood corpuscles and that in birds this function is chiefly displayed by the endothelium of the sinusoids of the liver. For the histological differentiation of the cells engaged in the red-blood-corpuscle destruction at a given time, Kyes used Perl's microchemical reaction to form Prussian blue with the haemoglobin-derived iron in the phagocytic cell, and to such macrophages as might thus be demonstrated to be actually destroying red blood corpuscles he applied the term *hemophages*.

Two years later the same author (2) showed that the hemophages are also the cells responsible for the prompt phagocytic removal of bacteria from the blood-stream of inoculated pigeons, and he concluded that this phagocytic destruction is so extensive and so rapid as to be a determining factor in the natural resistance of birds to the pneumococcus.

Riddle (3) in 1921 observed the correspondence between the location of the commoner tuberculous lesions in pigeons and the location of the hemophages described by Kyes. He concluded that phagocytic localization of the tubercle bacilli by hemophages determined the sites of the lesions in avian tuberculosis occurring spontaneously in pigeons and agreed with the findings of Moore and Ward (4), Edwards (5), Vosgien (6), Hastings, Halpin and Beach (7) and Van Es and Schalk (8), that the liver is the organ most frequently and indeed almost invariably involved in these animals.

From these combined findings it appeared probable that a highly favorable opportunity for the study of fixed-tissue phagocytosis of tubercle bacilli would be afforded in the observation of the fate of these bacilli in the liver of birds where large numbers of highly active hemophages are demonstrable by differential histological methods.

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This latter point was taken to be of no little importance, since, in previous observations by Nathan (9), Oppenheimer (10) and Evans, Bowman and Winternitz (11), concerning the relation of tubercle bacilli to liver endothelium, use was made of a mammal, usually the rabbit, and in order to obtain sufficient identification of the fixed-tissue phagocytes in such species, complicating injections of colloidal pigments were necessary, either prior to or coincident with the injection of the bacilli. This left for interpretation the rôle of each of two phagocytized reagents in relation to the phagocyte itself. In the use of the pigeon, however, injection of only the tubercle bacilli would be required, the identification of the hemophages being attained by a microchemical reaction subsequent to tissue-fixation.

With the information above mentioned as a background, I injected groups of pigeons intravenously with selected strains of tubercle bacilli, and killed the birds in subgroups at various fixed time-periods subsequent to the injection, the first period being ten minutes after injection and the last, thirty-two weeks.

Immediately after the death of a given bird, small pieces of liver were placed for four hours in Zenker's fluid without acetic acid. They were rinsed in distilled water and passed through 60, 85 and 95 per cent and absolute alcohol, being allowed to remain from one-half to one hour in each. Embedded in paraffin, the tissue was sectioned at five micra.

Suitably stained, the sections were studied microscopically, with special reference to (1) the number of tubercle bacilli in the liver at the several periods following injection, (2) the relation of the tubercle bacilli to phagocytic cells, (3) evidence of tubercle-bacillus destruction, (4) morphological changes indicative of a cellular reaction to the bacilli on the part of hemophages and the parenchymatous tissue of the liver, and (5) any contrast in results following the use of pathogenic avian tubercle bacilli and that of human tubercle bacilli, to the latter of which pigeons are insusceptible.

The tubercle bacilli used for injection in the particular experiments to be discussed in detail, were of two avian and two human strains. The designation and history of each strain is as follows:

Human, R1: Bacillus tuberculosis hominis. "Isolated in 1891 directly from the human lung, the patient having died from acute miliary tuberculosis. . . . Its virulence for rabbits and guinea pigs was pronounced at first but at present the culture barely infects guinea pigs, even in large doses, and then only very slight localized or chronic disease results." (Paterson (12).)

Human, H37: "Isolated August 12, 1905, directly from the sputum on Hesse's agar, the

source being a case of chronic tuberculosis. The culture was of average virulence for guinea pigs, but produced in rabbits only local nodules at site of inoculation subcutaneously, and fibrous foci in calves intravenously." (Paterson, *l.c.*)

Avian, A.T.C.118: This culture of avian tubercle bacilli was obtained from the American Type Collection, but further history it is lacking other than that it was originally obtained from the U. S. Army Medical Museum.

Smith Avian V: This culture was obtained from Theobald Smith, who isolated it from a stork in 1912.

Subcultures of these strains were grown upon glycerinated veal-agar at 37°C. The cultures were at all times wrapped in tinfoil and transplants were made monthly when growth warranted. For injection the microörganisms were suspended in physiological salt solution as given in detail later.

The method of tissue-fixation has been stated. The staining method chiefly employed was as follows:

Five-micron sections were stained forty-eight hours in carbol-fuchsin at room temperature and decolorized with 25 per cent aqueous solution of sulphuric acid. The sections were next deeply stained with acid-carmine and quickly rinsed in alcohol. To evoke a prussian-blue reaction with the ferric-iron content of the hemophages, the slides were then immersed for ten minutes in a bath composed of 9 parts of a 2 per cent aqueous solution of potassium ferrocyanide (C. P.) and 1 part of a 5 per cent aqueous solution of hydrochloric acid. If the prussian-blue reaction was not apparent under the low power of the microscope at the end of the ten minutes, the sections were rinsed in a 1 per cent aqueous solution of hydrochloric acid to which a few drops of hydrogen peroxide were added. The specimens were next rinsed in distilled water, dehydrated with alcohol, cleared and mounted in unrefined Canada balsam.[2] Additional preparations were stained with carbol-fuchsin alone, with Mallory's connective-tissue stain and with haematoxylin and eosin.

The first group of pigeons, 32 in number, were injected intravenously with a suspension of the nonvirulent human tubercle bacilli, R1. The suspension was made by adding the well-developed growth of five relatively young cultures (about 4 weeks) on glycerine-veal-agar to 50 cc. of physiological salt solution and shaking the mixture with glass beads for one-half hour. Upon standing thirty minutes after shaking, the mixture resolved into a distinct sediment of larger clumps of bacilli among the glass beads and a supernatant even suspension of dispersed microörganisms. One cubic centimetre of the supernatant suspension was injected into the leg-vein of each pigeon without attendant symptoms. The birds of the series were killed in triplicate after 10 minutes, 3 hours, 12 hours, 2 days, 4 days, 10 days, 20 days, 40 days and 81 days.

Microscopic study was first made of sections of livers stained with

[2] In most so called neutral balsams, prussian-blue loses its color in a relatively short time through a reduction process.

carbol-fuchsin alone to determine the relative number of tubercle bacilli present in that organ at the various times subsequent to injection. The results, although difficult to express in exact quantitative terms, were very definite. As an approximate quantitative method of comparison, 20 fields (Zeiss comp. oc. no. 6; apochr. obj. 1–12, num. ap. 1.25; tube 120 mm.) per section were studied for each liver, and the approximate number of microörganisms present listed according to the following notation:

A field containing one bacillus or two separated bacilli was designated by a single plus sign (+); a field showing a clump of bacilli (3 or more), by two plus signs (++); a field showing one clump and one or two scattered bacilli, by three plus signs (+++); and a field showing two or more clumps, with or without additional scattered bacilli, was designated by four plus signs (++++). This system was necessitated by the fact that the microörganisms, as herded within the macrophages to form the clumps, are too densely packed to be counted individually. When the tabulation for the 20 fields of a given specimen was completed, the results were totalled in terms of exponents of + ($+^{10}$, $+^{40}$, etc.). When no microorganisms were present in 20 fields, the result was indicated by zero (0).

In the series of pigeons under discussion, which had received the nonvirulent R1, the relative number of bacilli found in the liver of the individual birds killed at the close of the various intervals of time following inoculation was as is shown in table 1.

TABLE 1

The relative incidence of human tubercle bacilli R1 in the livers of pigeons killed at varying time-intervals subsequent to injection

LAPSE OF TIME.....	10 MINUTES	1 HOUR	3 HOURS	12 HOURS	2 DAYS	4 DAYS	5 DAYS	10 DAYS	20 DAYS	40 DAYS	81 DAYS
	$+^{8}$	$+^{22}$	$+^{20}$	$+^{6}$	$+^{6}$	$+^{3}$	$+^{4}$	$+^{7}$	$+^{2}$	$+^{1}$	0
	$+^{30}$	$+^{24}$	$+^{19}$	$+^{19}$	0	0	$+^{4}$	$+^{5}$	$+^{6}$	$+^{2}$	0
	$+^{12}$	$+^{18}$	$+^{15}$	$+^{9}$	0	0	$+^{5}$	0	$+^{10}$	0	—
Average of 3 birds....	$+^{17}$	$+^{21}$	$+^{18}$	$+^{11}$	$+^{2}$	$+^{1}$	$+^{4}$	$+^{4}$	$+^{6}$	$+^{1}$	0

As indicated in table 1 many microörganisms were present in the liver ten minutes after injection, and approximately the same number was present for three hours. The rapid progressive destruction of the microorganisms is indicated in the relative number of bacilli seen in the 3-hour, 12-hour and 2-day intervals. The latter and all subsequent periods except the last show a residuum of bacilli. It is to be noted from the data given in table 1, that the first four time-periods roughly constitute one group, in which there is relatively a large number of microörganisms

present, in contrast to a second group comprising the remainder of the time-periods in which there is a relative paucity of tubercle bacilli.

The next studies of this series concerned the more exact relation of the contained bacilli to the liver tissues. Sections were prepared in which the hemophages were differentiated by the prussian-blue reaction as given above, and it was at once apparent that the localization of the tubercle bacilli in the liver is a phenomenon of hemophage phagocytosis. Even as early as ten minutes following injection, fully three-quarters of the microörganisms contained within the liver are included within the prussian-blue-differentiated hemophages, and in the birds killed one hour or more after injection practically no bacilli were found in any other location. Therefore, both in rate and extent the hemophage phagocytosis of tubercle bacilli approximates that described by Kyes (*l.c.*) for the pneumococcus.

A given hemophage, as seen in these sections, contains anywhere from a single bacillus to a mass of 30 or 40 bacilli, so closely packed in a vacuole of the cytoplasm that their exact number cannot be determined. The hemophage may at the same time contain a recently ingested erythrocyte displaying a normal nuclear and cytoplasmic staining reaction.

In the series under discussion, as in others to be considered later, the maximum number of tubercle bacilli phagocytically localized in the liver is observed in the birds killed one and three hours following intravenous injection. The decrease in the number of contained microörganisms, which is already apparent in the "12-hour" liver, is distinctly due to the destruction of the tubercle bacilli within the hemophages. A large proportion of the included microörganisms at this time show marked changes in staining reaction and in contour. Certain bacilli stain as beaded filaments, others intensely as homogeneous ovoid bodies, while others are but slightly tinted by the stain. In the "2-day" livers the number of microörganisms is still further reduced and, in addition to the disintegration forms described above, there may be seen a finely granular detritus, which stains with the carbol-fuchsin.

Throughout the active process of ingestion and digestion of the tubercle bacilli by the hemophages, the hemophages themselves are modified in form. They are of increased size, and the unattached margin bulges markedly into the capillary lumen. The nucleus increases in size and stains less intensely. It is often roughly triangular in section, but in this series displays no anomalous tendency to divide.

Following the destruction of the tubercle bacilli within a given hemo-

phage, the cell decreases in volume, becoming flatter, and its nucleus smaller, and finally it presents the appearance of hemophages in the normal liver.

These changes in the hemophages are the only tissue reactions observed in the liver of the birds in this experiment (human, R1).

The conclusion drawn from the results of this first series of injections is that when suspended nonvirulent human tubercle bacilli are introduced intravenously into pigeons large numbers of bacilli are rapidly localized in the liver by inclusion within the hemophages of Kyes and are for the most part promptly digested by these cells. The tissue reaction in the liver is limited to changes on the part of the hemophages.

As already stated, the human tubercle bacilli used in the first experiment were of the nonvirulent group, judged by guinea-pig pathogenicity. In the second experiment human tubercle bacilli of relatively high virulence (H37) were employed. Except for the virulence of the bacilli used, the terms of the experiment were essentially similar to those of the first. Forty-eight pigeons were inoculated intravenously and killed in triplicate at subsequent time periods up to thirty-two weeks.

Table 2 gives a comparison of the number of virulent tubercle bacilli (H37) observed in the liver of birds at various periods following injection.

TABLE 2

Relative incidence of virulent human tubercle bacilli (H37) in the livers of pigeons killed at varying time-intervals subsequent to injection

LAPSE OF TIME.....	10 MINUTES	30 MINUTES	1 HOUR	3 HOURS	6 HOURS	18 HOURS	42 HOURS	72 HOURS	96 HOURS	112 HOURS	7 DAYS	14 DAYS	21 DAYS	49 DAYS	84 DAYS	224 DAYS
	+26	+40	+20	+31	+13	+18	+15	+18	+6	+8	+5	+1	0	0	0	0
	+13	+32	+28	+40	+38	+34	+6	+17	+12	+7	+9	+4	0	0	0	0
	+40	+35	+18	+15	+13	+14	+8	+15	+17	+11	+11	+4	0	0	0	0
Average of 3 birds.....	+26	+36	+22	+29	+21	+22	+10	+17	+12	+9	+8	+3	0	0	0	0

A third experiment paralleled the above two; in it, however, avian tubercle bacilli were used instead of the human type. The avian bacilli were of a nonvirulent strain (*A.T.C.*118), and the amount injected as near that used in the preceding experiments as the method permitted. Forty-six birds were used in this series. The results obtained were the same as those seen in the first two experiments, except that the complete

destruction of the bacilli on the basis of a twenty-field count required a somewhat longer time.

A comparison of the number of microörganisms at the various periods is given in table 3.

TABLE 3

The relative incidence of nonvirulent avian tubercle bacilli (A. T. C. 118) in the livers of pigeons killed at varying time-intervals subsequent to injection

LAPSE OF TIME..	10 MINUTES	30 MINUTES	1 HOUR	3 HOURS	6 HOURS	18 HOURS	42 HOURS	72 HOURS	96 HOURS	112 HOURS	7 DAYS	14 DAYS	21 DAYS	49 DAYS	84 DAYS	168 DAYS
	+42	+7	+40	+60	+80	+70	+40	+32	+21	+12	+24	+25	+2	0	0	0
	+30	+11	+80	+70	+80	+48	+30	+30	+35	+28	+33	+1	+20	0	0	0
	+38	+28	+50	+60	+60	+48	+40	+26	+30	+36	+54	+10	+3	+1		
Average of 3 birds...	+37	+15	+56	+63	+73	+55	+36	+25	+28	+25	+37	+12	+8	+3	0	0

The three experiments given above show no sharp contrast; regardless of the strain of tubercle bacilli used, the rate of destruction is approximately the same. In considering the tables submitted, too much emphasis should not be placed upon minor differences. The methods of making the bacterial suspensions and of determining the number of microörganisms in the liver are both very limited from the point of view of exact quantitative determinations. The gross results however are accurate and distinct. They show that the greatest number of tubercle bacilli are present in the liver within a few hours after intravenous injection and that the number of bacilli gradually decreases until at the end of a few weeks, at most, no microörganisms remain.

The histological findings are the same in all of the three experiments. The bacilli localized in the liver are intracellular within hemophages and are destroyed within these cells. The fixed-tissue reaction is limited to transient changes in the hemophages during their activity in phagocytosis and digestion of the tubercle bacilli. There is no evidence that the bacilli are in any degree more resistant to the digesting action of the hemophages than are other bacteria, such as pneumococci.

The fourth experiment, next to be reported, contrasts with those already given in that relatively large doses of *virulent* avian tubercle bacilli were injected with a view of provoking a maximum reaction in the host. Except for the number of bacilli inoculated and their virulence, the same methods were used as in the previous experiments. The strain

of bacilli employed was Smith Avian V, and by prolonged and intensive shaking a suspension was obtained, in which the number of bacilli was from four to five times as great as in the previous instances. Forty-eight pigeons were injected intravenously, each with 1 cc. of the suspension, and no acute symptoms followed the inoculation. The birds were killed in triplicate at stated periods and the livers studied as above.

The number of bacilli observed in livers of the birds killed within two days of injection was very great. In the "72-hour" livers the microorganisms were already reduced one-half in number, but no further marked reduction was seen in the "1-" and "2-week" livers. In the "3-week" livers, however, practically all of the bacilli had been destroyed. In the "6-week" birds no microörganisms were found in the livers of two of the birds, and, but a single bacillus in the liver of the third pigeon. Here, as in the previous experiments, there is seen in the liver a progressive destruction of tubercle bacilli, which at the end of six weeks is practically complete.

Table 4 gives a comparison of the number of bacilli found in the livers of birds killed at several of the periods following injection.

TABLE 4

The relative incidence of virulent avian tubercle bacilli (Smith Avian V) in the livers of pigeons killed at varying time-intervals subsequent to the injection

LAPSE OF TIME.....	30 MINUTES	6 HOURS	42 HOURS	72 HOURS	7 DAYS	14 DAYS	21 DAYS	42 DAYS	175 DAYS
	+160	+160	+160	+80	+80	+60	+2	0	0
	+160	+160	+160	+80	+67	+10	+1	+1	0
	+160	+160	+160	+80	+73	+60	+6	0	
Average of 3 birds.....	+160	+160	+160	+80	+73	+43	+3	0(n)	0

(n) one single bacillus found in examination of one of the livers of the birds killed at this time period.

Although no marked contrast was found as between the general rate of destruction of the virulent avian tubercle bacilli in the liver in the last experiment and the destruction of human and nonvirulent avian strains in the previous experiments, very distinct differences were observed as to the morphological changes in the liver. It has already been stated that the injection of the human and nonvirulent avian strains did not produce tissue reactions in the liver other than transient changes in the hemophages. Following the injection of the virulent avian strain in the present series, however, there occurred giant-cell formation, the production of tubercles, and a definite increase in connective tissue.

The detailed histological study of these changes will be presented in a subsequent paper.[3]

In contrast to the findings of Evans, Bowman and Wintermitz (*l.c.*) no evidence of mitosis was observed in the hemophages participating in giant-cell formation. Also, no phagocytosis of the tubercle bacilli by microphages was observed.

CONCLUSIONS

The major conclusions to be drawn from the results of this investigation are:

1. The intravenous injection of tubercle bacilli into pigeons results in rapid and extensive localization of the bacilli in the liver. This localization is accomplished by the phagocytic action of the vascular endothelium constituting the intima of the venous sinusoids.

2. The great bulk of the tubercle bacilli thus localized are digested within the phagocytic cells very rapidly, there being no evidence that tubercle bacilli are more resistant to digestion than are other bacteria, notably the pneumococcus.

3. Except in those instances in which enormous numbers of bacilli are injected, no morphological changes result in the liver other than those displayed by the hemophages.

4. When large doses of virulent avian tubercle bacilli are injected, permanent tissue changes do occur which include the formation of tubercles and giant cells.

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[3] It may be stated at this time that Kyes, employing the prussian-blue reaction, has found that the giant cells and certain other cells of tubercles in the liver give the same microchemical reaction for iron as do the endothelial hemophages, indicating the origin of the former cells from the latter. (*Personal communication.*)

THE VALUE OF ROUTINE FLUOROSCOPIC EXAMINATIONS OF THE CHEST AMONG INDUSTRIAL EMPLOYEES

H. H. FELLOWS[1] AND W. H. ORDWAY[2]

The Metropolitan Life Insurance Company Sanatorium at Mt. McGregor, New York, which is maintained for the employees of the Metropolitan Life Insurance Company, receives annually 34 per cent of its cases from the Home Office of the Company in New York City, where approximately 11,000 of their 45,000 employees in the United States and Canada are at work. In a period of ten years 16 per cent of the admissions received from our Home Office have been tuberculous. In the year 1926 forty-eight persons and during the first ten months of 1927 seventy-two individuals from the Home-Office group were admitted to the Sanatorium suffering from pulmonary tuberculosis. Of these 120 patients, 40 were classified as incipient and 70 as advanced. Of those with advanced lesions 22 had been employed one year or less.

All applicants for employment are examined physically, as well as questioned regarding their personal and family history, before acceptance, and those with physical defects of major importance are rejected. Since there are a number who, within a year after acceptance for employment, are diagnosed as having advanced tuberculosis, it was suspected that cases of unrecognized tuberculosis were being accepted in spite of rigid physical examinations and careful questioning.

Casting about for a more accurate means of detecting latent disease and filtering out the cases which, because of unrecognized physical signs, were accepted for employment, the writers decided to obtain the services of skilled fluoroscopists, *well trained* in this type of work, and to subject each applicant to a fluoroscopic examination of the chest after the history had been taken and the physical examination completed. This method has been in use with the last 800 applicants. Those who by fluoroscope are seen to have questionable or definite pathological changes, are X-rayed, stereoscopic chest-films being taken. From these 800 applicants

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accepted after history and physical examination, 8 cases of well developed pulmonary tuberculosis have been found by fluoroscopic examination. Two of these showed calcified lesions, while 6 were classified as being potential prospects for Sanatorium care. Furthermore, physical examinations of the chests of these applicants shown by X-ray to have definite tuberculosis, and reëxamined by trained physicians, well qualified to diagnose tuberculous lesions, failed with two exceptions to give abnormal chest-signs.

Since X-rays of the lungs do not reproduce well in print, and in order to give some idea of the extent of the lesions found, the X-ray interpretations are given below as pertinent examples of the type of case segregated by fluoroscopic examination.

1: Right Lung: Definite invasion of the mid-zone by the thickened trunks from the hilum region, definite parenchymal changes, rather scattered in type but somewhat fluffy, invading the first and second interspaces. Obliteration of the costodiaphragmatic angle.

Left Lung: Definite thickening of the first interspace and paravertebral trunks, both reaching out to the extreme periphery. The paravertebral blending with a scattered mottling seen at the extreme apex.

Impression: Incipient tuberculosis, R.I.L.I.

2: Right Lung: Definitely exaggerated root region. Definite parenchymatous infiltration, scattered throughout the upper third, extending to the third rib and sixth vertebral spine. There are also slight parenchymal changes seen in the circle of the fourth interspace near the mid-zone.

Left Lung: Hilum exaggerated somewhat. Slight beading and thickening of the trunks radiating from the root region. At the extreme apex slightly thickened pleural cap.

Impression: Incipient tuberculosis, R.I.

3: Right Lung: Root region exaggerated. Marked peribronchial thickening and radiation from the root region toward the apex, especially the paravertebral, first-interspace and second-interspace trunks. At the apex a definite patch of mottling, rather soft and fluffy in type, occupying the circle of the first interspace near the periphery. There is also a small amount of mottling beneath the thickened pleural cap.

Left Lung: Definite thickening of the paravertebral and first-interspace trunks, the paravertebral reaching to the extreme apex, where they blend with a slight though definite lessened transmission of ray occupying the extreme apex and reaching to the clavicle and third vertebral spine. There is slight

thickening of the pleural cap. In the circle of the tenth rib near the periphery there is a large calcified density.

Impression: Incipient tuberculosis, R.I. Questionable, L.I.

We believe that a wider experience with this means of examination will prove of distinct value in diagnosis, and may have its application in various clinics, X-raying all cases which have suspicious findings on fluoroscopic examination. We have been greatly gratified to find how small a lesion can be discovered by the fluoroscope, and are convinced that this method of examination with large groups of persons is going to bring to light many cases which later break down with active tuberculosis.

In this preliminary report, even with a relatively small experience, it is not too early to state that the fluoroscopic examination of chests made by well-trained physicians, experienced in this type of work, does detect tuberculous lesions which otherwise are unrecognized by physical examination alone. This method of examination is rapid, economical and accurate, and it is hoped that with added experience its application in preventive and industrial medicine will be demonstrated.

THE WHITE BLOOD CELLS IN HUMAN TUBERCULOSIS

AS STUDIED BY THE SUPRAVITAL TECHNIQUE[1,2]

R. S. CUNNINGHAM AND EDNA H. TOMPKINS

When in 1921 Sabin (14) adapted Pappenheim's method of staining red blood cells to the study of the leucocytes, she inaugurated a new era in blood technique, characterized particularly by the fact that the cells were studied while alive instead of after fixation. This technique has been found to be particularly helpful in the differentiation of the cells of the monocytic group from those of the lymphocytic group, inasmuch as the differences between the two types of cells are much more marked in this technique than in any other hitherto devised. By means of this more exact method for the discrimination of these cells, Sabin, Doan and Cunningham (16), in a study of the mononuclear cells composing the tubercle, found, for the first time, evidence that the typical epithelioid cells of this structure are formed from monocytes. This observation and the added accuracy gained by the application of the supravital technique to the study of the circulating mononuclear cells naturally led to renewed interest in the blood, already so often studied, in tuberculosis, and to observations upon it from new and fruitful angles.

Cunningham, Sabin, Sugiyama and Kindwall (6) made the first routine study of tuberculosis by means of this technique. They inoculated rabbits with bovine tubercle bacilli and found that the monocytes were both stimulated and changed in phagocytic activity, that they increased in numbers as the disease progressed, and that they decreased during periods of recession in the disease, while the lymphocytes responded in inverse manner. They also found tubercle bacilli apparently living within the monocytes, and particularly within the modified monocytes or epithelioid cells. They therefore advanced the concept that the tubercle bacilli are able to stimulate the production of monocytes in increased numbers and are in turn phagocytized by these cells, which appar-

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ently in many instances are unable to digest them. In that case, if this concept is true, bacilli continue to live and multiply within these cells, which, therefore, upon their death, liberate viable microörganisms.

In a different animal species, the guinea pig, similar findings have been obtained in this laboratory by Cunningham, *et al.* (7). These animals were inoculated with human tubercle bacilli and it was found that the numbers of circulating monocytes increased while those of lymphocytes decreased as the disease progressed; and in the diseased tissues masses of monocytes in all stages of development toward the epithelioid cell, and many of them having viable bacilli within their cytoplasm, were found. These animals succumbed more quickly and with less extensive pathological lesions than did the rabbits referred to above. At the same time the blood of normal control guinea pigs showed higher values for monocytes and lymphocytes than did that of normal rabbits. It seems possible that the more rapid decline of the guinea pigs with tuberculosis is connected with the higher normal level of monocytes and a greater susceptibility of the lymphocytes to tuberculo-toxins than is true in rabbits.

These observations on the blood of rabbits and guinea pigs and the importance of the explanations suggested for them naturally raised the query as to whether the changes found are characteristic of other species of animals infected with tuberculosis, and in particular whether they occur in the blood in human cases of the disease.

LITERATURE

The comment is often made that the less a disease is understood the more abundant are the descriptions of it. Certainly it is true in tuberculosis that, in conformity with the little that is known concerning the nature and treatment of the disease, the literature abounds with reports upon the blood cytology, and the relationship of the red blood cells, total white blood cells, the neutrophiles, the Arneth index, the eosinophiles and the lymphocytes to the state of the infection. Observations upon the monocytes, however, are relatively few. The general consensus of opinion derived from these reports is that the lymphocytes, and, to a less extent, the eosinophiles, are an index of resistance and are high in uncomplicated cases, while, on the other hand, elevations above normal of the white blood count and of the neutrophiles, and a movement of the Arneth index to the left, are unfavorable manifestations in the

clinical course, and are usually accompanied by a decrease in numbers of lymphocytes and eosinophiles. Achard and Loeper (1) in 1900 found the mononuclear cells, in which they included both the lymphocytes and the granular mononuclear cells, elevated in human tuberculosis. Claude and Zaky (5) in 1902 and Halbron (8) in 1903 stated that the total white cell counts increase and the eosinophiles and lymphocytes decrease with clinical regression. Steffen (18) in 1910 reported upon 75 cases of human tuberculosis and found the total white blood count increased in severe cases and the lymphocytes and eosinophiles increased in milder ones. Miller and Reed (10) in 1912 and Baer and Engelsmann (3) in 1913 obtained similar results, besides observing that a shift of the Arneth index to the left was an unfavorable indication. On the other hand, Wack (20) in 1914 and Peters (12) in 1919, in a study of 34 cases of lymphatic tuberculosis, found the absolute number of lymphocytes low, and the latter also found a normal number of total white blood cells and regarded the eosinophiles as of no significance. Blumenfeld (4) in 1919 considered that the lymphocytes are high in tuberculosis. In 1920 Riedel (13) reported upon cases of bone and joint infection in agreement with Steffen's findings for miscellaneous tuberculous infections, and, in addition, found that the lymphocytes rise following ultraviolet treatment.

Recently Schittenhelm (17) in an exhaustive review drew the same conclusion as his predecessors, that a decrease in lymphocytes and eosinophiles, a rise in total count and a movement of the Arneth index to the left are unfavorable clinical manifestations in a tuberculous infection. He reported that there is no change in the blood in lymphatic tuberculosis until it becomes generalized. Tanaka (19), on the other hand, found no change in the numbers of lymphocytes, eosinophiles or neutrophiles in tuberculosis, although he concluded that the total white blood count is elevated and the Arneth index shifts to the left. Murphy (11) in 1926 remarked that a parallelism exists between lymphoid activity and resistance to tuberculosis. Finally, in 1927, Baldwin, Petroff and Gardner (2) have reviewed the literature with the same conclusions as Schittenhelm, except that they give perhaps less diagnostic and prognostic weight to the changes found in the blood in human tuberculosis.

Concerning the monocytes, the literature affords far fewer studies, and these of much less value. This may in part be the result of the fact that the findings reported were obtained by use of one or another of the older forms of staining technique, in which accurate differentiation of monocytes from other mononuclear cells is difficult.

In reports by Achard and Loeper (1) and by Webb and Williams (21) mononuclear cells are said to be increased, but there is no differentiation between lymphocytes and monocytes. Claude and Zaky (5) found the transitional and large mononuclear cells to be slightly increased in five cases of tuberculosis, in three of which there was still greater elevation after treatment; and Halbron (8) showed that these cells were increased above normal in nearly all of the 21 cases which he studied. In the 79 cases reported by Steffen (18) the transitional cells are tabulated, but no comments are made upon them and in no instances do they reach a value above 9 per cent, nor is there any difference observed in their numbers in acute and mild cases. Baer and Engelsmann (3) reported that the transitional cells increase with altitude, but that neither they nor the large mononuclear cells change with the clinical variations in a tuberculosis patient. In 8 cases Wack (20) tabulated the differential figures for the transitional and the large mononuclear cells together, and reported no value above 8 per cent. In the 34 cases of lymphatic tuberculosis which he analyzed, Peters (12) concluded that the mononuclear cells are slightly elevated. Riedel (13) found no clinical relationship to the numbers of transitional and large mononuclear cells in his studies upon bone and joint cases. Tanaka (19) reported that there was no change in the transitional cells, but that the large mononuclears increased from an average of 3 per cent in the normal to 3.8 per cent in tuberculosis cases. Schittenhelm (17) in his recent review drew the conclusion that the large mononuclear and mast cells in the blood of tuberculosis patients are of no importance. No reports could be found upon studies of living blood cells in human tuberculosis.

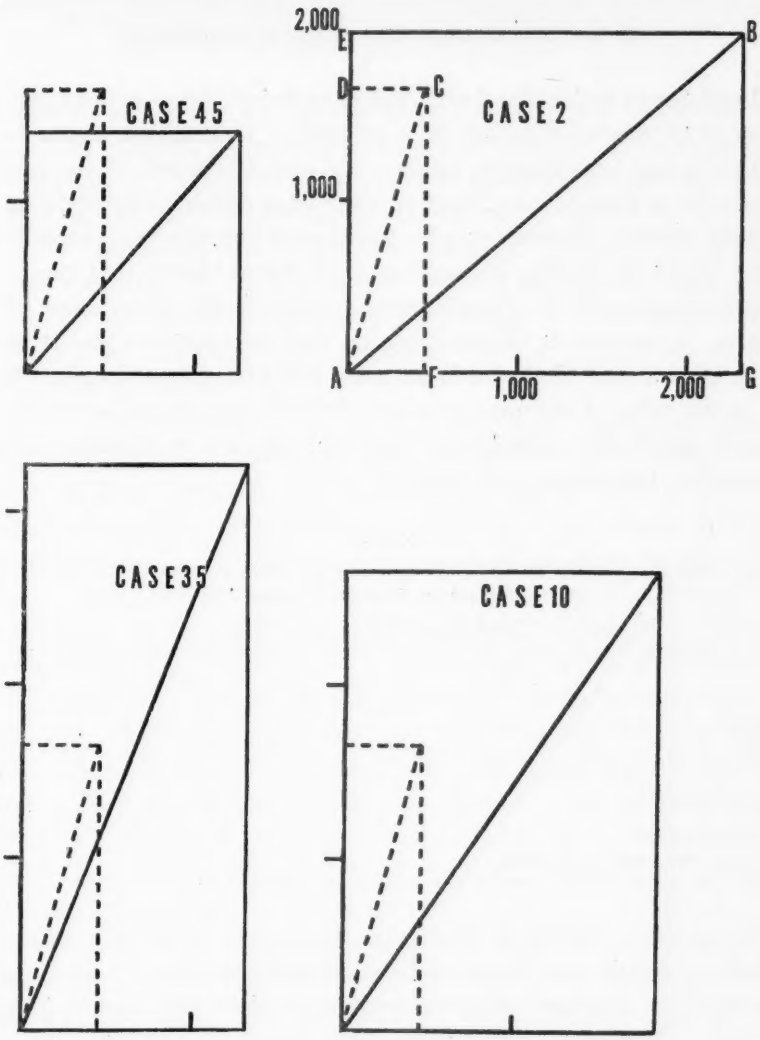
This failure of the literature to reveal conclusive findings concerned with the mononuclear cells in human tuberculosis, corresponding to the characteristic findings in those cells in the infection in rabbits and guinea pigs, made it seem advisable to analyze the blood in clinical cases of tuberculosis by means of the supravital technique. Accordingly, during the past year, we have made such a study upon the general-ward cases of tuberculous infection in the Vanderbilt University Hospital. We started the study purely from the experimental standpoint, that is, to determine what changes might occur in the blood in human tuberculosis. While the very definite findings obtained have led to an expansion of the investigation to include the problems of differential diagnosis (which will be communicated at a later date when more data are obtained) the scope of this report remains as at the start. It deals simply with the cytological findings in the blood and exudates from cases of human tuberculosis.

METHODS

These cases have been studied soon after entry and before the diagnosis of tuberculosis was more than suspected, and were taken without regard to site of infection, severity or age. Later they were divided into two groups, those in which the various clinical findings were such as to make the final ward diagnosis of tuberculosis one of reasonable certainty, and those upon which a definite clinical diagnosis was never made, but whose blood findings agreed with those given by definite cases of tuberculosis. For the most part, the cases studied remained in the hospital but a short time before discharge to home or institution for chronic cases, and, while they frequently were of a chronic type clinically, they were inmates of this institution too briefly to be followed as chronic cases. The few that did remain long enough were very profitably followed, and it is to be regretted that more studies, over a long period of time, could not be made, as they might well reveal factors, both in regard to failure and increase of resistance, not discovered by single observations. Whenever possible, exudates and tissue obtained at biopsy were also analyzed by the same methods as the blood. Among our series of cases there was only one death in the hospital; autopsies were therefore not studied.

The differential counts were all made by the supravital technique of Sabin. The smears were allowed to remain in contact with the stain in the hot-box for about twenty minutes before examination. It was found that normal monocytes do not adequately stain when exposed for a shorter period to the dye and in that case they may be easily overlooked. Longer staining gives a false impression of the phagocytic activity, but within a reasonable length of time it in no way interferes with an accurate differential count. Activity of the monocytes was also gauged in relation to that of the polymorphonuclear leucocytes which had, of course, stood for the same length of time, and a monocyte was judged as overactive if it contained more neutral-red droplets than usual when compared to those of the polymorphonuclear cells. This question of phagocytic activity is important, inasmuch as the findings on animals show that the monocytes are not only increased in number but that their quantity and quality of phagocytosis is modified by infection with tuberculosis. Total white blood counts were also made in most instances, and were used in conjunction with the differential counts to obtain the absolute numbers of the various cellular entities.

The findings thus obtained in the blood were analyzed in regard to the



GRAPHS REPRESENTING THE FINDINGS IN THE MONOCYTES, LYMPHOCYTES AND RATIOS OF CASES 2, 10, 35 AND 45

The graph of case 2 is lettered for purposes of explanation

Explanation of graph for case 2

The dotted lines give graph of the average normal (table 1); the solid lines give graph of the case.

CF represents absolute number of lymphocytes of normal.
BG represents absolute number of lymphocytes of case.
DC represents absolute number of monocytes of normal.
EB represents absolute number of monocytes of case.
AC represents ratio line of normal.
AB represents ratio line of case and moves clockwise as the ratio increases.
The normal ratio is directly proportional to $< DAC$.
The case ratio is directly proportional to $< DAB$.

total number of white blood cells and of each individual type of cell and in regard to their qualitative characteristics. In addition, it was found of interest and assistance to analyze the count in terms of the ratio of monocytes to lymphocytes, that is, the factor obtained by dividing the absolute number of monocytes by the absolute number of lymphocytes. In the report on rabbits, it was shown, as stated above, that the monocytes increased and the lymphocytes decreased with progression of the disease. It was due to this observation that our attention was attracted to the importance of the ratio between the two types of cells. While this is the ratio of absolute numbers of monocytes to those of lymphocytes, it may be more simply computed by comparison of the percentages obtained in the differential counts.

TABLE 1

Average white blood counts obtained from six normal adults by repeated studies (see Sabin, Cunningham, Doan and Kindwall)

Total white blood count = 8270

CELLS	PERCENTAGE	ABSOLUTE NUMBERS
P.M.N.	68.4	5,657
P.M.E.	4.4	363
P.M.B.	1.2	99
Total lymphocytes	19.7	1,629
Total monocytes	5.7	471
Ratio of monocytes to lymphocytes	0.3	

The absolute values of monocytes, lymphocytes, and the monocyte-lymphocyte ratio were found to be more easily understood when plotted graphically. Examples of these graphs are given for cases 2, 3, 10, 35 and 45. The graph on case 2 has been labelled for the purpose of explanation. The graph is made by plotting the lymphocytes along the ordinates and the monocytes along the abscissae, and determining the point of intersection of these coördinates; from this point to the origin a diagonal is drawn and the position of this line represents the ratio between monocytes and lymphocytes. Each graph is composed of two figures; the one for the tuberculosis case is given in solid lines, and the one for the average normal human blood in dotted lines.

Three factors may thus be read and compared with the normal in each graph; these are the absolute number of monocytes along the abscissae, the absolute number of lymphocytes along the ordinates, and the ratio

between these two types of cells by the angles formed by the intersection of the diagonals with the coördinates at the origin. The diagonal line representing the case moves to the right of the line representing the normal when the ratio is above normal and to the left when it is below normal. The angle which the normal diagonal line makes with that of the patient gives an estimate of the grade of discrepancy between the normal and pathological ratios, since this angle and the ratio which it represents become greater and greater as the line moves away from the normal in any direction.

For a normal standard of human blood as a comparison with the figures obtained on tuberculosis cases, averages were computed from the values published by Sabin, Cunningham, Doan and Kindwall (15) in their study of the normal rhythm of the white blood cells in a series of 6 normal adults. The averages thus obtained are given in table 1.

Our cases, in which there was no doubt as to the clinical diagnosis of tuberculosis, have been analyzed, arranged and numbered according to the grade of clinical severity and according to the site of infection (table 2). The more severe cases are listed first and therefore fall into the lower numbers. Those cases, in which a definite diagnosis was never established, but in which the blood gave findings similar to those in tuberculosis cases, have been listed separately in table 3. The individual values for the different factors given in table 2 have been analyzed against each other and against the clinical severity of the case and site of infection.

Intracutaneous tuberculin tests were made upon a certain proportion of the cases. In the adults these were done with three strengths only, 0.001, 0.01 and 0.1 mgm. per cc. The O.T. put up by the H. K. Mulford Company was used, and the dilutions made in physiological saline solution. Two days were allowed between each test, and the tests were begun with the lowest strength, and carried through to the higher ones only when reactions did not occur with the strengths previously used. For children, the tests were made by the pediatric service directly. They were performed in much the same way, only they were carried through to higher strengths and with a different preparation of O.T. At the same time a number of miscellaneous cases were similarily tested. These findings have been analyzed against the clinical severity and the various factors of the blood.

TABLE 2

Cases with definite diagnosis of tuberculosis arranged according to clinical severity

CASES NUMBERED ACCORDING TO SEVERITY*	COMPLETE DIAGNOSIS	TUBERCULIN REACTION (MGM. O.T. PER 1 CC.)			BLOOD							REMARKS
							Lymphocytes		Monocytes			
		0.001	0.01	0.1	Date	W.B.C.	Per cent	Total	Per cent	Total	Ratio	
1	Tuberculosis of cerebral meninges Staphylococcus-aureus abscess face Staphylococcus-aureus abscess forearm	0	0	0		13,600	13.0	1,768	6.0	816	0.5	Spinal fluid showed high percentage of lymphocytes and of monocytes, some of which were stimulated. Supravital stain.
2 P	Tuberculous bronchopneumonia Acute miliary tuberculosis Congenital club-hand			+		27,400	7.0	1,918	8.5	2,329	1.2	
3	Pulmonary tuberculosis Tuberculous pneumonia				10– 9–26	12,000	16.5	1,980	10.0	1,200	0.6	
					10–28–26	4,080	10.5	428	20.0	816	1.9	
					11– 1–26	18,160	1.5	272	4.5	817	3.0	
					11– 8–26	10,060	4.0	402	15.5	1,559	3.9	
					11–26–26	19,400	6.0	1,164	8.0	1,552	1.6	
					12–20–26	10,400	9.5	988	7.0	728	0.7	
					1–10–27	11,320	6.1	691	10.0	1,132	1.6	
		0	+		1–31–27	11,560	6.5	751	12.0	1,387	1.8	
		+			2–21–27	9,600	13.0	1,248	12.5	1,200	1.0	
		+++			3–26–27	7,600	14.5	1,102	17.0	1,292	1.2	
					4–30–27	11,400	7.5	855	8.0	912	1.1	
					6–23–27	7,840	10.5	823	11.0	862	1.0	

4	Chronic pulmonary tuberculosis, far advanced				8– 9–26		14.5		13.3		0.9	
					8–16–26		17.0		23.0		1.4	
5	Vincent's angina Chronic pulmonary tuberculosis, far advanced					11,200	10.0	1,120	19.5	2,184	1.9	
6	Chronic pulmonary tuberculosis, far advanced Pneumothorax				10–28–26	12,680	13.0	1,648	8.5	1,078	0.7	
					11–26–26	16,560	5.4	894	9.7	1,230	1.8	
7	Diabetes mellitus Gangrene of foot Chronic pulmonary tuberculosis, far advanced Chronic nephritis. Cataract.	+			3–26–27	12,320	11.0	1,355	9.5	1,170	0.9	
					4– 2–27	15,000	6.5	975	12.0	1,800	1.8	
8 P	Chronic pulmonary tuberculosis, moderately advanced Tuberculosis of larynx Phlyctenular conjunctivitis Undernutrition			±		8,800	12.5	1,100	27.5	2,420	2.2	
9	Serofibrinous pleurisy Chronic pulmonary tuberculosis, moderately advanced (?) Chronic tonsillitis	++				9,880	16.5	1,630	19.0	1,877	1.2	Pleural fluid showed many lymphocytes and monocytes of an epithelioid type. Supravital stain.
10	Chronic pulmonary tuberculosis, moderately advanced Serofibrinous pleurisy					10,600	25.0	2,650	17.5	1,855	0.7	Pleural fluid showed a high percentage of lymphocytes and monocytes of epithelioid type. Supravital stain.

TABLE 2—*Continued*

CASES NUMBERED ACCORDING TO SEVERITY*	COMPLETE DIAGNOSIS	TUBERCULIN REACTION (MGM. O.T. PER 1 CC.)			BLOOD							REMARKS
							Lymphocytes		Monocytes			
		0.001	0.01	0.1	Date	W.B.C.	Per cent	Total	Per cent	Total	Ratio	
11	Pulmonary tuberculosis	++				10,680	31.5	3,364	13.5	1,442	0.4	
12 P	Chronic pulmonary tuberculosis, moderately advanced Tuberculosis of pleura with effusion Chronic tonsillitis. Adenoids. Caries of teeth Chronic myositis, cervical			+		7,200	12.5	900	18.0	1,298	1.4	
13 P	Chronic pulmonary tuberculosis, moderately advanced Tuberculosis of peritoneum Tuberculosis of epiphysis with abscess Chronic nephritis. Congenital syphilis.			+		8,040	21.0	1,688	14.0	1,126	0.6	Peritoneal fluid characteristic of tuberculous fluids. Fixed stain.
14	Pulmonary tuberculosis, moderately advanced				7- 1-26 8-12-26	7,280	12.5 27.0	910	14.0 15.0	1,019	1.1 0.6	
15	Chronic pulmonary tuberculosis, moderately advanced Syphilis Chronic gonococcal urethritis, male urethra	+				6,800	24.5	1,666	14.5	986	0.6	

	urethra											
16	Chronic pulmonary tuberculosis, moderately advanced Bilateral inguinal hernia, indirect Varicocele, left	+			2– 1–27 2– 2–27	8,760 9,640	17.5 14.0	1,533 1,349	9.0 10.0	788 964	0.5 0.5	
17	Serofibrinous pleurisy Chronic pulmonary tuberculosis, moderately advanced (?)	+				7,120	12.0	854	13.0	926	1.1	
18	Acute fibrinous pleurisy Bronchopneumonia, group undetermined Chronic pulmonary tuberculosis, moderately advanced Acute laryngitis	0				11,560	11.5	1,329	6.5	751	0.6	
19	Chronic pulmonary tuberculosis, moderately advanced					5,320	30.0	1,596	14.0	744	0.5	
20	Composite tumor, parotid region Chronic pulmonary tuberculosis, moderately advanced Bronchopneumonia Gangrene of lung					15,960	5.0	798	4.5	718	0.9	
21	Serofibrinous pleurisy Chronic pulmonary tuberculosis, moderately advanced (?) Ulcer of duodenum		+			7,120	20.0	1,424	8.0	570	0.4	Chest fluid showed high percentage lymphocytes and monocytes. Supravital stain.
22	Chronic pulmonary tuberculosis, moderately advanced					14,400	13.5	1,944	3.5	504	0.3	

TABLE 2—*Continued*

CASES NUMBERED ACCORDING TO SEVERITY*	COMPLETE DIAGNOSIS	TUBERCULIN REACTION (MGM. O.T. PER 1 CC.)			BLOOD							REMARKS
		0.001	0.01	0.1	Date	W.B.C.	Lymphocytes		Monocytes		Ratio	
							Per cent	Total	Per cent	Total		
23	Serofibrinous pleurisy Chronic pulmonary tuberculosis, moderately advanced Cardiac hypertrophy and insufficiency					3,400	20.5	697	14.0	476	0.7	
24	Chronic multiple arthritis Chronic pulmonary tuberculosis, moderately advanced Leukoderma					7,680	19.0	1,459	5.5	422	0.3	
25	Chronic pulmonary tuberculosis, incipient	+				12,360	19.0	2,348	7.0	865	0.4	
26	Acute multiple arthritis Chronic pulmonary tuberculosis, incipient					10,080	13.5	1,361	18.0	1,814	1.3	
27 P	Erythema nodosum Chronic pulmonary tuberculosis, incipient Chronic tonsillitis; adenoids		+			10,640	19.0	2,022	11.0	1,170	0.5	

28 P	Vincent's angina. Tuberculosis of skin Chronic pulmonary tuberculosis incipient Tuberculosis of cervical lymph nodes Chronic tonsillitis			+		6,000	10.5	630	15.5	930	1.5	
29	Chronic pulmonary tuberculosis, incipient Acute fibrinous pleurisy Maxillary sinusitis					5,800	13.5	783	19.5	1,131	1.4	
30	Chronic pulmonary tuberculosis, incipient Alveolar abscesses, chronic, multiple Arthritis					7,880	16.0	1,261	11.5	906	0.7	
31	Chronic pulmonary tuberculosis, incipient Syphilis					6,600	28.5	1,881	12.0	792	0.4	
32	Chronic rheumatic endocarditis Chronic valvular cardiac disease Chronic pulmonary tuberculosis, incipient	+			5–11–27 5–21–27	6,600 6,960	25.0 31.0	1,650 2,158	8.5 17.0	561 1,183	0.3 0.5	
33	Chronic pulmonary tuberculosis, incipient		+		8–26–26 8–30–26	12,400 11,160	18.0 11.0	2,239 1,228	4.0 5.0	498 558	0.2 0.5	
34	Syphilis. Chronic gonococcal endocervicitis. Serofibrinous pleurisy Chronic pulmonary tuberculosis, incipient (?) Pneumothorax					6,440	15.0	966	6.5	419	0.5	Pleural fluid showed high percentage of lymphocytes and monocytes of epithelioid type. Supravital stain.

TABLE 2—*Continued*

CASES NUMBERED ACCORDING TO SEVERITY*	COMPLETE DIAGNOSIS	TUBERCULIN REACTION (MGM. O.T. PER 1 CC.)			BLOOD							REMARKS
							Lymphocytes		Monocytes			
		0.001	0.01	0.1	Date	W.B.C.	Per cent	Total	Per cent	Total	Ratio	
35	Chronic pulmonary tuberculosis, arrested Migraine. Alveolar abscess.					10,520	31.0	3,261	12.5	1,315	0.4	
36	Constitutional inferiority Chronic pulmonary tuberculosis, arrested					7,360	24.0	1,766	6.5	478	0.3	
37	Chronic pulmonary tuberculosis, arrested Asthma Chronic fibrinous pleurisy Chronic bronchitis. Bronchopneumonia					13,200	18.5	2,442	11.0	1,452	0.6	
38	Serofibrinous pleurisy Pulmonary tuberculosis (?) Tuberculosis of cervical lymph nodes Chronic gonococcal urethritis	+				7,160	11.0	788	18.0	1,289	1.7	Aspiration fluids of suprasternal cyst and of pleural cavity showed high percentage of lymphocytes and epithelioid type monocytes. Supravital stain.
39	Chronic pulmonary tuberculosis, quiescent Tuberculosis of caecum (?)					7,120	19.5	1,388	10.0	712	0.5	

40	Acute fibrinous pleurisy Syphilis					9,640	12.1	1,157	11.0	1,060	0.9	Adenitis, probably tuberculous, developed after discharge from hospital
41	Chronic tonsillitis. Fibroid tuberculosis. Orthostatic albuminuria Acute laryngitis	+				7,800	14.0	1,092	9.0	702	0.7	
42	Tuberculosis of lymph nodes, general Tuberculosis of kidneys (?)	0	0	0		14,000	18.5	2,590	18.5	2,590	1.0	
43	Tuberculosis of cervical lymph nodes	+				14,320	14.0	2,005	15.5	2,220	1.1	
44 P	Chronic tonsillitis			+	9–23–26		10.0		5.0		0.5	
	Tuberculosis of cervical lymph nodes				9–30–26		12.5		10.0		0.8	
	Tuberculosis of pleura with effusion				10– 1–26	11,320	13.5	1,528	12.0	1,358	0.9	
45	Tuberculosis of cervical lymph nodes	++				10,440	13.5	1,409	12.0	1,253	0.9	Biopsy; lymph node, characteristic tuberculosis. Fixed stain.
46	Tuberculosis of cervical lymph nodes Chronic tonsillitis. Adenoids. Acute pharyngitis	+				9,800	11.5	1,127	5.5	539	0.5	Biopsy, lymph node, characteristic tuberculosis. Fixed stain.

TABLE 2—*Concluded*

CASES NUMBERED ACCORDING TO SEVERITY*	COMPLETE DIAGNOSIS	TUBERCULIN REACTION (MGM. O.T. PER 1 CC.)			BLOOD							REMARKS
							Lymphocytes		Monocytes			
		0.001	0.01	0.1	Date	W.B.C.	Per cent	Total	Per cent	Total	Ratio	
47	Tuberculosis of cervical lymph nodes	+				7,720	26.0	2,007	6.5	501	0.3	Biopsy, lymph nodes, characteristic tuberculosis. Fixed stain.
48 P	Vincent's angina. Chronic tonsillitis.			+	11– 2–26	5,920	17.0	1,006	11.5	681	0.6	
	Tuberculosis of hilum				11–12–26	12,320	21.0	2,587	9.0	1,109	0.4	
49 P	Dacryocystitis					7,200	26.5	1,908	12.5	900	0.5	
50	Erythema multiforme	0	0	0		7,000	23.0	1,610	10.0	700	0.4	
	Alveolar abscess. Maxillary sinusitis (?)											
51	Phlyctenular keratitis (?)					13,240	8.0	1,059	7.5	1,027	0.9	
	Otitis media. Abscess of arm											
52	Tuberculosis of lymph nodes (?)				6–23–27		19.0		22.0		1.2	
	Phlyctenular conjunctivitis (?)				6–26–27		19.5		14.5		0.7	
53	Tuberculosis of 7th and 8th dorsal vertebrae					8,920	3.5	312	9.0	803	2.6	Biopsy; bone, characteristic tuberculosis. Fixed stain.
	Tuberculosis of hip joint											

54	Tuberculosis of ribs. Tuberculosis of sternum.	+				8,120	19.0	1,543	9.0	733	0.5	
55	Tuberculosis of costal cartilage (?)					13,161	7.0	921	5.5	724	0.8	Pus in abscess at operation considered characteristic of tuberculosis
56	Tuberculosis of lumbar and dorsal vertebrae Tuberculosis of (post.) mediastinum (?)	+				7,880	19.5	1,537	9.0	709	0.5	

* *P* signifies that case was on the pediatric service.

TABLE 3

Cases with questionable diagnosis in which the blood gives the same findings as in tuberculosis

CASE NUMBER*	COMPLETE DIAGNOSIS	TUBERCULIN REACTION (MGM. O.T. PER 1 CC.)			BLOOD							REMARKS
		0.001	0.01	0.1	Date	W.B.C.	Lymphocytes		Monocytes		Ratio	
							Per cent	Total	Per cent	Total		
57	Chronic bronchitis Chronic infection of lungs Haemangioma of neck Syphilis					12,320	7.0	856	13.0	1,590	1.8	
58	Fracture of rib Traumatic pneumothorax Haemothorax					11,600	11.5	2,334	10.5	1,218	0.9	
59	Serofibrinous pleurisy Syphilis (Pulmonary tuberculosis?)	+				6,080	14.5	881	19.0	1,155	1.3	Pleural fluid showed high percentage of lymphocytes and monocytes. Supravital stain.
60	Fever, unknown cause					6,840	20.0	1,368	16.5	1,129	0.8	
61	Diabetes mellitus Lung tumor				11–17–27 11–19–27	12,520	21.5 23.5	2,692	9.5 10.0	1,127	0.4	
62	Lung tumor (?) Diabetes mellitus Gangrene				1– 4–27 1–21–27	10,480 10,960	19.0 5.5	1,991 603	8.5 9.5	891 1,041	0.4 1.7	

63	Syphilis (?) of meninges Meningitis Congenital cardiac disease					16,120	3.0	4,833	6.0	966	0.2	Spinal fluid showed high percentage of lymphocytes and monocytes. Supravital stain.
64	Mediastinal tumor Paralysis of nerve VII Iritis Chronic tonsillitis				10– 4–27 11–20–27	9,600 10,000	16.0 16.0	1,536 1,600	10.0 8.0	960 800	0.6 0.5	
65	Acute fibrinous pleurisy					10,720	21.5	2,305	7.5	804	0.3	
66	Carcinoma of lung Cardiac hypertrophy					9,360	21.0	1,966	8.5	796	0.4	
67	Abscess, psoas muscle and thigh	++				6,120	18.0	1,101	13.0	596	0.7	
68	Bronchitis. Emphysema. Bronchiectasis Chronic myocarditis						10.0		13.0		1.3	
69	Sarcoma of mediastinum with metastases to bones Chronic nephritis Arthritis of spine						8.5		21.5		2.5	
70	Acute fibrinous pleurisy, diaphragmatic						15.5		15.5		1.0	
71 P	Chronic adhesive pleurisy. Abscess of brain			0			4.0		12.0		3.0	

* *P* signifies that case was on the pediatric service.

FINDINGS

It has been found, as may be seen from the 56 cases reported in table 2, upon which the diagnosis of tuberculosis was definite, that the total white blood counts were elevated in about one-half of the cases; and that, on the whole, the higher values were found in the cases of greater clinical severity, the same cases usually showing the higher number of monocytes and the higher ratios. In fact, rarely was a count above the normal 8,000 found in a mild case. The total white blood count seems to bear very little relationship to the number of lymphocytes, and practically none to age or site of infection. In view of the fact that the higher values were found in the more severe cases, it is to be expected that, in cases observed over any length of time, lower white blood counts will occur when the clinical status is good than when it is unfavorable. And such was found to be the case. As the clinical status improved the white blood count decreased and at the same time, as might also be expected, this diminution corresponded to a diminution in both monocytes and ratio, and to an elevation in lymphocytes. These features were especially marked in cases 3, 6 and 7.

Contrary to numerous reports in the literature, the lymphocytes proved to be elevated in only one-third of the cases. In fact, on the whole, they were below normal, although the milder cases (30 to 56) rarely showed lymphocytes below 1,000. In accord with the earlier writers, however, the lower values in our findings tended to occur in the more severe cases, as, for example, cases 3, 12, 14, 17, 20, etc., and, in any one case, to decrease with the occurrence of untoward symptoms (cases 3, 6 and 7). Concomitant with these decreases in the lymphocytes, the monocytes, the ratio and the white blood counts tended to rise. While the lymphocytes showed a certain tendency to a reciprocal relationship with the monocytes, this was by no means an invariable relationship, and not infrequently the highest lymphocytic values occurred in those cases with the highest number of monocytes. When the lymphocytes were elevated they were usually more phagocytic than normal, as judged by the unusual amount of dark staining neutral-red which they contained in their cytoplasmic vacuoles. It is interesting to observe that children showed no greater tendency to higher lymphocytic values in this disease than did adults, and, in fact, gave some of the lowest figures obtained (see cases 8, 12 and 48). This is contrary to the usual observation that, in infectious diseases in children, the lymphocytes tend

to be markedly elevated. When one considers the high lymphocytic values that ordinarily occur in childhood, the low values found in tuberculosis represent relatively a greater diminution than occurs in adults. At the same time, too, the cases of lymphatic tuberculosis also showed lower lymphocytic values than their excellent clinical state would indicate, and these same cases gave higher monocytic and ratio values than would be expected; as is shown, for instance in cases 44, 45 and 46. Despite the fact that the lymphocytes were in general below normal, there are cases in which, if not above normal, they were at least higher than would be expected from comparison with other clinical cases. Those cases numbered 7, 10, 11, 16, 25, 27, 31, 33, 35 and 37 belong in this group. These were all cases of pulmonary tuberculosis. It may easily be that the judgment of the grade of clinical severity was in error, but it is interesting to speculate concerning the possibility that the resistance, as evidenced by the numbers of circulating lymphocytes, may be greater in pulmonary tuberculosis than in infections elsewhere.

The findings in regard to the monocytes were far more consistent than those concerning the lymphocytes. In the first place, the monocytes were elevated in number in all but three cases. Moreover, they were modified in the very characteristic manner described by Cunningham, Sabin, Sugiyama and Kindwall; the vacuoles of neutral-red were fine and greatly multiplied in number, and they had a tendency toward arrangement into rosette formation. In other words, they approached the epithelioid type of cell. Not only were they increased in number and stimulated in activity, but the grade of elevation agreed fairly well with the grade of clinical severity, as is shown by the fact that the higher monocytic values occur with the lower-case numbers, which represent the more severe cases clinically. There is an exception to this statement, however, in the fact that cases of bone and lymph-node infections (see cases 38, 42, 43, 44, 45, 53, 54 and 55) showed elevation of the monocytes and, at the same time, of ratio, and also a fall in lymphocytes out of proportion to the expectation from the clinical severity. Also there were a few other cases (26 and 37), which showed values higher than were to be expected from the clinical status, but these were, however, complicated by the presence of other disease entities. Not only did the monocytes, with these exceptions, follow very closely the grade of clinical severity in individual determinations from case to case, but in those cases followed over a considerable period of time the monocytes paralleled well, in

their increases and decreases, the coincidental and similar changes in the severity of infection (cases 3, 6 and 7). And moreover, in such instances, the ratios and total white blood cell counts usually rose or fell accordingly, while the numbers of lymphocytes changed in the opposite direction. In fact, the monocytes fairly closely accompanied similar changes in the ratio. While the monocytes were elevated in all but three instances, this elevation was slight in the milder cases, in which an absolute number above 800 cells was rarely encountered. It was observed that children (cases 2, 8, 12, 13, 27 and 44) on the whole, and the cases of lymph-node infection (cases 38, 42, 43, 44 and 45) gave the higher values, while these same cases showed a tendency to low lymphocytic values. This reciprocal relationship between these two types of cells was undoubtedly not an accidental finding, and yet it is by no means an invariable one. It showed best in the repeated observations upon individual cases (cases 3, 6 and 7) or in comparison of one type of tuberculous infection with another, for instance, lymphatic compared with pulmonary tuberculosis. In single observations upon a series of miscellaneous cases, the reciprocal relationship is often not in evidence.

The ratio is a factor of the monocytes and lymphocytes, and so very naturally showed correlation with the changes in those cells. Since the monocytes were practically always elevated, it was not surprising to find that the ratio was elevated in all but three cases. And where the monocytes were low, that is, in the group of mild cases with values below 800, the ratio was usually moderately below unity (cases 39, 41, 46, 47 and 48), and averaged about 0.5. In the more severe cases (cases 2, 5, 9, 14, 17, etc.) it was usually close to or above unity, but, since it is dependent upon the lymphocytes also, it was low in those cases in which the lymphocytes remained high despite the elevation of the monocytes (cases 10, 11, 13 and 15). Also, in accord with the tendency to parallelism with the increases and decreases of monocytes, it mounted during the unfavorable periods in any single case (cases 3, 6 and 7) and was high in those more severe cases, which likewise showed high monocytic values. The exception to this, as in the case of the monocytes, is the group of lymph-node cases (cases 38, 42, 43, 44 and 45). These, as stated above, showed higher monocytic and lower lymphocytic figures than was expected. The relationship of the ratio to lymphocytes was far less marked than that to the monocytes, except that, in general, the higher ratios occurred in those

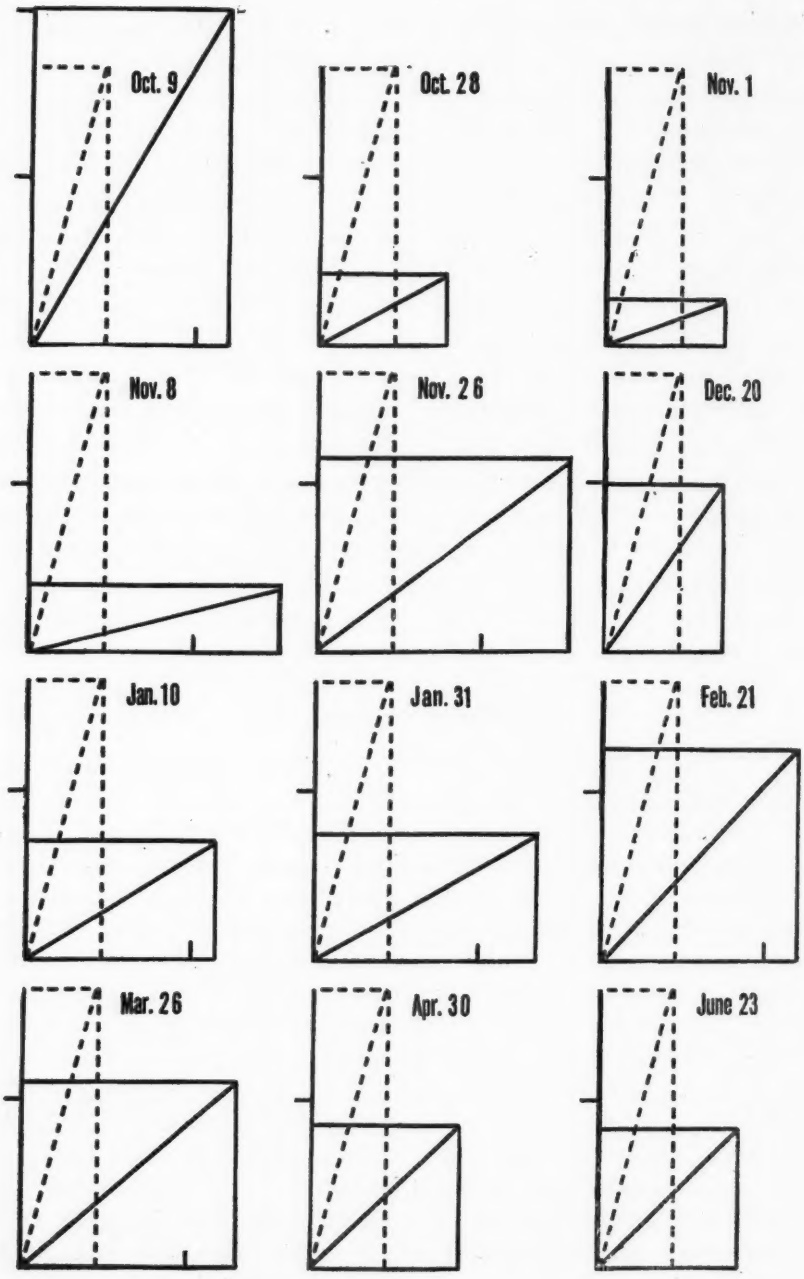
cases in which the lymphocytes were low (cases 5, 8, 12, 14, etc.), and that, in any single case (cases 3, 6 and 7), the rise in ratio was usually accompanied by a fall in lymphocytes, which was concomitant with greater clinical severity and a rise in the monocytes.

These complicated relationships are more easily understood from the graphs. As stated previously, there are three factors expressed in them, total monocytes, total lymphocytes and the ratio between these two. It is unnecessary to discuss in detail the findings as shown on the graphs, as such findings have already been given in detail in regard to the separate factors of which the graphs are composed.

Cases 3, 6, 7, 14, 32, 33, 44, 48 and 52 were studied over periods of time varying from three days to nine months. Most of these cases were patients who showed sharp clinical changes during a relatively short stay in the hospital, rather than the changes of the chronic course so characteristic of sanatorium cases. Case 3 was followed over the longest period of time. The graphs representing the findings in the blood of this case show the changes from date to date in relation to those in the clinical course which is abstracted below. Abstracts are also given for the clinical histories of cases 6 and 7.

Case Reports

Case 3: Female, Japanese, 29, married, housewife. Admitted October 3, 1926. *Complaint:* Cough with sputum; hoarseness. *Family History:* Husband reported to have healed tuberculosis. *Past History:* "Pleurisy" 10 years ago, fluid removed from chest at that time; "catarrh," left lung, 2 years ago. *Present Illness:* Onset 2 months before entry; began with a cold following exposure. *Physical Examination:* Signs in both lungs characteristic of bronchitis rather than tuberculosis. Acid-fast bacilli in sputum. General condition excellent. *Clinical Course while in Hospital: October 3 to 19:* Temperature normal. No changes in condition from those at entry. *October 19:* One tooth extracted under novocaine. Marked temperature elevation a few hours later. *October 21:* Temperature still elevated to 104°F. X-ray showed many calcified lymph nodes in left upper chest and suggestion of fibroid tuberculosis. *October 22:* Signs of pneumonia, left lung. *October 23:* X-ray showed mottling of both lungs, but more marked on left. *October 19 to 30:* Temperature constantly 100°–104°F. *October 29:* Signs of pleurisy and fluid, left chest. Signs of pneumonia continued. Pneumococcus, type III, isolated from sputum. No fluid obtained from chest-tap. *October 30 to November 20:* Condition grave. Complete suppression of function of left lung. Temperature constantly 100°–105°F. X-ray plates November 2 and 12 showed increased mottling of left



GRAPHS REPRESENTING THE FINDINGS IN THE MONOCYTES, LYMPHOCYTES AND RATIOS OF CASE 3 AT VARYING PERIODS OF THE CLINICAL COURSE

See abstract of case 3

lung, but no consolidation. *November 22 to December 20:* Condition better. Temperature 100°–104°F. X-ray plate on November 23 showed complete consolidation of left lung, as did plates repeated on December 6, December 20, January 4 and January 25. Physical signs showed no change. *December 22 to February 14:* Improvement continued. Temperature stayed between 99° and 102°F. X-ray plates of February 2 and February 17 showed slight increase in penetration of left chest. On February 7 acid-fast bacilli were found for the first time since the onset of acute symptoms on October 19. Physical signs showed no change. Tuberculin reaction was negative to a strength of 0.001 mgm. per cc., but positive after 0.01 mgm. on January 28. *February 21 to April 18:* Temperature remained normal. Moderate clearing in physical signs. General condition improved. Sat up April 15. X-ray plates showed no changes. *March 26:* Tuberculin reaction strongly positive to 0.001 mgm. and on April 7 it was mildly positive to 0.0001 mgm. *April 18 to May 6:* Temperature elevated between 98° and 102°F. Chills and fever and leucocytosis during this time. No definite changes in general condition or in physical signs. *May 6:* Temperature became normal and has remained so ever since. Steady improvement in general condition. Slow clearing in the physical signs of consolidation. X-ray plates of June 28 and July 27 showed increased penetration on left, but no definite areas of normal lung markings. The tuberculin reaction remained positive to 0.0001 mgm. on July 25, but had not increased in intensity, and no reaction was obtained to 0.00001 mgm. per 1 cc. Patient ambulatory.

Case 6: Female, white, 30, single, no occupation. Admitted October 28, 1926. *Complaint:* Cough, hoarseness, night-sweats, expectoration. *Family History:* Father died with tuberculosis 14 years ago. *Past History:* Influenza with slow recovery 8 years ago. *Present Illness:* Acute symptoms for 1 month. Six years ago noted unproductive cough and fatigue. Two years ago pain, left side, and productive cough which has persisted to date. Eighteen months ago night-sweats began. Fifteen months ago diagnosed as tuberculous and sent to a sanatorium which she soon left. Her condition remained the same until 1 month ago, when the previous symptoms became exacerbated and marked dyspnoea developed. *Physical Examination:* Signs of tuberculosis in left lung. General condition moderately good. No evidence of involvement of right lung, nor of cavity formation. Acid-fast bacilli in sputum. X-ray showed coarse fibroid tuberculosis, with small amount activity, scattered over left lung and upper part of right apex. *Clinical Course while in Hospital: October 28 to November 26:* Rest in bed. No change in condition from that at entry. Temperature not elevated. *November 26:* Artificial pneumothorax begun on left and repeated at various intervals until January 1, 1927. Temperature continued normal. *November 26 to January 1:* General condition

unchanged, but some loss in weight. Cough decreased. X-ray plates showed small cavities, left apex, and partial left pneumothorax. Temperature normal throughout. Discharged to sanatorium.

Case 7: Female, white, 66, married, housewife. Admitted March 26, 1927. *Complaint:* Weakness, malaria, blisters on feet. *Family History:* Unessential. *Past History:* Unessential. *Physical Examination:* Signs of tuberculosis, both uppers. Findings indicative of diabetes. Acid-fast microörganisms in sputum. Signs of gangrene of foot. X-ray findings "indicative" of active tuberculosis, right lung, with cavity at apex. Temperature normal. General nutrition and condition poor. *Clinical Course while in Hospital:* Remained in hospital only one week, in which time her diet was regulated for diabetes and the gangrene of the foot improved. There was no improvement in the pulmonary condition.

It was seen in the study of case 3, and it was true also of the other patients whose course could be followed, that with increased severity of the clinical state the monocytes and ratio increased and the lymphocytes decreased. The total white blood counts became elevated in such instances, and were accompanied by secondary infection. These changes in the blood were so consistent in relation to the clinical changes, that it was equally possible to predict the clinical status from the blood findings or *vice versa*. Therefore, the changes in the blood were valuable from a prognostic and diagnostic standpoint.

The findings upon children are indicated in the table by the letter *P* (pediatric) beside the case number, and have been considered in the individual discussion concerning lymphocytes, monocytes, ratios and total counts. It may be stated that no different relationship from that in adults was found in either ratio or total counts. On the other hand, in the case of the lymphocytes (cases 2, 8, 12, 13, 28, 44, 48 and 49), while the absolute values varied little from those found in the adults, the degree of diminution, when one considers the normally high lymphocytic values in childhood, was considerably greater than in adults with the same grade of clinical involvement. Moreover, the monocytes (cases 2, 8, 12, 13, 27, 28, 44, 48 and 49) quite definitely, and out of all proportion to the degree of clinical severity, inclined to the higher values in the cases of tuberculosis in children. Therefore, the inverse relationship between monocytes and lymphocytes, that has been shown elsewhere, is unusually prominent in these cases of childhood infection.

The findings in relation to the site of infection have been given in

detail in the individual discussion of the findings in lymphocytes, monocytes, ratios and total counts. It need only be reiterated that in the cases with pulmonary involvement the clinical severity was fairly consistent with the rise in monocytes, ratio and white blood cells, and, to a smaller extent, with the fall in lymphocytes; while in lymph-node infections the changes in those same factors were out of porportion to the clinical severity, as was also the case in tuberculosis in childhood and in the few bone infections among our cases. The studies upon infections in other localities than these were too few to warrant any conclusions.

In only a few instances in this series of cases were exudates obtained for study, but in every instance in which they were obtained the preparations with neutral-red showed a characteristic increase in the monocytic cells over that found in other than tuberculous fluids. Moreover, these cells were usually of the epithelioid type. At the same time, there was always the high percentage of lymphocytes, which is so characteristic of exudates in chronic diseases such as tuberculosis. As is to be expected when the monocytes and lymphocytes are high, there were practically no polymorphonuclear cells. The total counts varied enormously according to the site of the exudate, but this did not seem to affect the character of the fluid, which remained the same in all cases. The fluids studied consisted of cystic (case 38), spinal (case 1), and pleural (cases 9, 10, 21, 34 and 38).

Due to the difficulty of obtaining at autopsy or biopsy material fresh enough for studying the cells in the living state, our results from the supravital staining of such material have been uncertain. In the animals studied by Cunningham, Sabin, Sugiyama and Kindwall the tissues were found to be infiltrated with monocytes and epithelioid cells. In our human cases, however, the cells were usually dead by the time the smears could be made, and therefore could not be differentiated by the supravital staining. Nothing can, therefore, be stated as to their living appearance. In the usual fixed preparations, however, according to the reports from the pathological departments, the lymph-node tissue obtained at biopsy upon cases 45, 46 and 47 had the characteristic appearance of tuberculosis, as did the bone obtained from case 53.

In analyzing the findings from the intracutaneous tests with tuberculin, it was found that of the 48 reactions positive to 0.001 mgm. only 16 cases were actively tuberculous, while of the 18 positive to 0.01 mgm. 3 cases were actively tuberculous, and of the 2 positive to 0.1 mgm. one

was actively tuberculous. In other words, of the 68 cases reacting, only 20 (that is, 30 per cent) showed clinical evidence of tuberculosis. In 100 cases studied in all, 32 showed no reaction. Of those showing no reaction, 4 were definitely cases of tuberculosis, and 2 had a severe grade of the disease. Case 3 showed decreased sensitivity during a crisis of tuberculous pneumonia and the sensitivity increased with improvement. These results obviously showed little relationship between the grade of clinical severity and that of reaction, except the suggestion that the strength of reaction diminishes when the clinical status is very severe. From the standpoint of the blood, no relationship was found between the strength of reaction and the individual factors of the blood.

DISCUSSION

From the above findings it is evident that very definite changes in numbers and character occur in the white blood cells in patients having tuberculosis. The most marked of these is in the monocytes, which are always increased and usually stimulated in a manner approaching the epithelioid type of cell. So invariable is the increase in the monocytes that it is of definite diagnostic value, and the diagnosis of tuberculosis would seem very doubtful in a case in which the blood showed no elevation of the monocytes. These increases in the monocytes also parallel the clinical status, both at the different periods of disease in one individual and between different individuals showing various grades of infection. In fact, they are so closely in accord with the clinical grade of infection, and so definitely increased when dissemination is occurring, that they may be regarded as an index of the extent of the anatomical lesion and therefore of dissemination. This reaction of the circulating monocytes to tuberculosis in the human being is so exactly in accord with that which has been found in animals that the cells probably have the same significance in the two instances. That is, if the theory outlined above is correct, that monocytes are capable of phagocytizing but are unable to destroy bacilli in tuberculous infections in animals, it is probable that they react in the same manner in tuberculosis of the human being. Bacilli have never been seen in circulating monocytes in the human being, but they have been seen in those of exudates, and this adds support to the probability that the monocytes have the same significance in the human being that they have in animals.

While the monocytes increase in infection, and seem to be an index of

dissemination and of the extent of the anatomical lesion, the lymphocytes, on the other hand, show a reciprocal relationship to the monocytes and seem to be an index of resistance. That they are an index of resistance is shown best in repeated examinations of the blood of an individual patient, in which case they increase during periods of recession of the infection and decrease as the disease progresses, while the monocytes change in the inverse manner. In a large group of miscellaneous cases, the patients who are more seriously ill will show the lower values for lymphocytes and at the same time the higher ones for monocytes. While there is no definite lymphocytic level below which one can say any given determination indicates failure of resistance, one can very definitely say that the patients showing a progressive decrease in lymphocytes are succumbing to the infection, and those with unusually high lymphocytic values have excellent combative powers. Murphy's investigations point to the same conclusion from a different point of view, inasmuch as he found that animals in which the lymphocytic production had been stimulated by various methods resisted tuberculous infections longer than did untreated animals.

There is a general tendency for the lymphocytes to be below normal in tuberculosis, which is in accord with the tendency of the disease to follow a chronically progressive course. This characteristic depression of lymphocytes is also in accord with the fact that the monocytes are practically always above normal; for just as these two types of cells change in opposite directions during the progress of the tuberculous infection in any one case, so naturally they tend to show a reciprocal relationship in the individual studies upon a series of cases.

The lymphocytes are low in lymph-node tuberculosis and also, when one considers the high lymphocytic values of normal blood in children, they are very low in tuberculosis of childhood. In these same cases, the monocytes are unusually high, which again illustrates the reciprocal relationship between these two types of cells.

Several possible explanations for this reciprocal relationship between monocytes and lymphocytes immediately occur to one. It may be that different etiological factors are in operation, one stimulating the monocytes, and another depressing the lymphocytes. It may be that the two types of cells are mutually antagonistic. The explanation may lie in the primitive origin of the cells, which may be stimulated by the tuberculous products to develop into monocytes instead of into lympho-

cytes. It may be that some specific toxin of tuberculosis is at once a stimulant to the monocytes and a depressant to the lymphocytes.

On the basis of the last of the explanations suggested above, it is possible to understand some of the confusing elements connected with the assumption that the lymphocytes are an index of resistance. The acceptance of a theory that relates the lymphocytes to resistance makes it difficult to understand why guinea pigs with high normal lymphocytic values, and children with active lymphogenic centres, are so susceptible to the infection; and why lymph-node invasion itself is so common, unless one assumes that tuberculosis produces a substance toxic to the lymphocytes. In that case, their numbers are an index of resistance, not on the basis that they control the infection, but on the basis that some inhibitive force checks the virulence of this toxicity upon the lymphocytes. In other words, with the conception that tuberculosis produces a lymphocytic toxin, the number of circulating lymphocytes is an index of the virulence of the infection; and therefore of the grade of resistance to it.

If we regard the monocytes as an index of dissemination and pathological lesion, and the lymphocytes as an index of resistance, then the ratio between these two types of cells gives, in mathematical form, an index of the relationship of the processes of infection to those of resistance and is high when the invasion is active. Without consideration of the absolute number of the cells, however, the ratio does not indicate the grade of the two opposing forces, but only their relationship to each other. In repeated observations upon a given case, it is an excellent figure upon which to judge improvement or recession. In practically all cases, it is above normal, which indicates, just as the tendency to low lymphocytes does, that in most tuberculous infections, invasion outruns resistance. It is high when the clinical status is unfavorable. With elevated monocytes, one may suspect tuberculosis. The numerical value of the ratio gives a measure for the resistance to the infection. By means of changes in the ratio one may judge the pathological events occurring in the progress of the disease.

The graphs, we have found, give a clearer estimate of these deviations from the normal in monocytes, lymphocytes and ratio than does any mathematical estimate alone. The graphs give, *en masse* as it were, the entire picture, the divergences in each specific factor in relation to those in the others, while mathematical figures alone concentrate the attention

upon one factor at a time. On the other hand, since the graphs are a composite of the three individual factors, these may, at will, be obtained separately. While the graphs are of great assistance in separate determinations upon different patients, their greatest service is in repeated studies upon the same patient, when the changes in the various factors may be read at a glance. In that case they represent, as figures alone cannot, to the average mind, the changes which have occurred in the patient's blood which are of significance in tuberculosis. The series of graphs upon patient no. 3 show this point especially well.

The findings concerning the mononuclear cells of the blood in tuberculosis and their significance have been discussed at length. In the granulocytic series, on the other hand, characteristic changes from the normal have not been found. The polymorphonuclear eosinophiles failed to be of the prognostic importance which previous reports promised. This disagreement with the earlier findings may lie in the fact that, in this part of the country, intestinal parasites occur sufficiently often to be a confusing factor in many of our cases. At any rate, no relationship was found between the polymorphonuclear eosinophiles and other factors of the blood or clinical findings. The total white blood cell counts bore no constant relationship to the individual cytological findings, nor to the clinical status. They were elevated at times, but in such instances secondary infections were often present, and in some of the most severe cases the counts remained practically normal. In fact, this tendency to a normal total count is so evident that it is of diagnostic value when used in conjunction with abnormalities in the mononuclear cells; and when the count is elevated in a tuberculous infection, it is most probable, in accord with Peters's conclusion, that a secondary infection has become superimposed upon the original tuberculous one.

It seems undoubted that in tuberculosis of the human being, as in animals, changes occur in the mononuclear cells of the blood, that is, in the monocytes and the lymphocytes, and in their relationship to each other, which are unfailing and characteristic, and are therefore diagnostic and prognostic in value. These changes almost invariably occur, but it is obviously of importance to determine whether they occur in other disease entities. While their absence contraindicates active tuberculosis, it may be that their presence does not necessarily indicate tuberculosis, and may give rise to confusion with other diseases that show similar changes in the blood. In fact, cases were met in which the blood picture was

quite similar to that found in tuberculosis. However, no cases have been observed to show an epithelioid type of monocyte except the tuberculous ones, but, on the other hand, all tuberculosis cases by no means show this characteristic change of the monocyte, even though the cells may be markedly increased in numbers. Therefore, while epithelioid cells are practically diagnostic of tuberculosis, the findings of increased monocytes, decreased lymphocytes and increased ratio, which nearly always occur in tuberculosis, may also appear in other conditions of disease and confuse the diagnosis.

This problem of differential diagnosis is now in process of study and will be reported upon later. While the diseases that, up to the present, have been found to be confusing, fall into specific groups, it is necessary to study additional examples of these groups, before definite statements can be made as to the instances in which confusion in diagnosis may occur, or as to the etiology of the changes in the blood in those instances. One series of cases, which have already somewhat differentiated themselves into a group, has, in common, some involvement of the liver, and this problem is being investigated both clinically and experimentally. Into this group fall cases of infectious jaundice, of arsphenamine poisoning, of purpura, of certain anaemias, of pneumonia, of some decompensated cardiac diseases, and of Malta fever, all of which have shown findings in the blood similar to those in tuberculosis. From the experimental standpoint other workers in the Department are finding that various chemicals which are toxic to the liver, such as carbon tetrachloride and tetrachlorethane, give similar findings in the blood.

It will be seen, therefore, that, while certain changes are always in evidence in the blood in tuberculosis, similar changes may occur in other conditions and these must be taken into consideration in making a diagnosis. On the other hand, monocytes of an epithelioid type have been seen nowhere but in tuberculosis.

While increases in monocytes and in ratio and decreases in lymphocytes may occur elsewhere than in tuberculosis, marked changes in these findings rarely occur quickly in tuberculosis, and this fact may possibly prove of diagnostic aid. In conditions other than tuberculosis changes in the blood frequently are marked and rapid, coincident with inauguration or removal of their cause.

Not only have the changes in the blood of tuberculosis patients been found to be characteristic, but tuberculous exudates studied by the

supravital staining showed a percentage of monocytes far above that found in any other type of exudate. This was true no matter what was the site of the exudate. Moreover, the monocytes were very definitely of an epithelioid type, which is practically pathognomonic. As a rule, the percentage of lymphocytes was also found to be high. Such findings, which, after all, are quite in accord with those in the blood, seem to be of definite diagnostic value when found in an exudate.

From the studies with tuberculin it is evident that the grade of reaction is not markedly, if at all, dependent upon any of the cellular elements of the blood nor to any marked degree upon the grade of clinical severity, since nearly all of the tuberculosis cases reacted to the weaker strength, regardless of clinical severity or grade of changes in the blood. Our few cases of tuberculosis that did not react correspond with the severe types that Hamman and Wolman (9) report as failing to respond to tuberculin, and the question arises as to whether the great decrease in lymphocytes in such cases is connected with this failure. Our results agree well with those of Hamman and Wolman, in that about 30 to 40 per cent of cases which react to tuberculin are not suffering from the disease, and also that only about 30 to 40 per cent of the hospital-ward population fails to react.

CONCLUSIONS

1. The findings in the white blood cells, when studied by the supravital technique, may be used in the diagnosis and prognosis of human tuberculosis.

2. The monocytes in the blood are practically always increased in number and stimulated in phagocytic ability in tuberculosis. These changes parallel the grade of clinical severity and are an index of anatomical extent of lesion and dissemination.

3. The lymphocytes in the blood are an index of resistance and parallel increased resistance.

4. The ratio of monocytes to lymphocytes is a useful mathematical expression for the extent of invasion compared to that of resistance. It is practically always elevated in tuberculosis and parallels increased clinical severity.

5. Graphs showing monocytes, lymphocytes and ratio give a rapid and clear estimation of these factors in the blood of tuberculosis patients.

6. Lymph-node tuberculosis tends to give higher monocytic and lower lymphocytic values than are indicated by the grade of clinical severity.

7. Children tend to show higher monocytic and lower lymphocytic values than are indicated by the grade of clinical severity.

8. Tuberculous exudates give a characteristic cell reaction, with high lymphocytic and monocytic counts. The monocytes tend to the epithelioid type of cell.

9. The strength of reaction to tuberculin bears no relationship to the findings in the blood in tuberculosis.

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STUDIES ON IMMUNITY TO TUBERCULOSIS

THE WANING OF CUTANEOUS HYPERSENSITIVENESS TO TUBERCULIN AND THE RELATION OF TUBERCULOIMMUNITY TO TUBERCULOALLERGY[1]

HENRY STUART WILLIS

The relation of cutaneous hypersensitiveness and its fluctuations to immunity in tuberculosis is an engaging question. It seems to be certain that the two phenomena exist only in the presence of tubercle and that each fluctuates alike with changes in the extent and intensity of the tuberculosis, or under various extraneous influences, such as fever, intercurrent infection, etc. Krause refers to immunity as its being perhaps a "function of allergy," in a paper (1) in which he summarizes relations between allergy and immunity as follows:

The "laws," if we may so call them, of specific immunity to tuberculosis, as worked out by many experimenters, during the last three decades, may be summarized as follows:

1. There is no specific immunity without preëxisting tubercle.
2. Immunity first appears with the palpable development of the focus.
3. It diminishes with the healing of the focus.
4. It disappears with the enucleation of the focus.
5. The degree of immunity varies directly with the virulence of the immunizing microörganism; or, otherwise expressed, with the amount of tubercle and activity of lesion in the host.

It is of the utmost significance that the circumstances of allergy exactly parallel those of specific immunity. . . . As regards allergy, we find that

1. It is never observed unless tubercle is present.
2. It appears coincidently with the establishment of lesion.
3. It diminishes as lesion heals.
4. It varies directly with the intensity of the disease, which in turn is dependent, not wholly, but in large measure on the virulence of the bacilli concerned.

[1] From the Kenneth Dows Tuberculosis Research Fund of the Johns Hopkins University and Hospital, Baltimore, Maryland.

How tuberculous infection confers immunity and allergy, or what the elements are that make for the allergic reaction, remains undisclosed. It has always been assumed that the protein of the tubercle bacillus is the sensitizing agent, and that it is the tuberculoprotein element in tuberculin or tubercle bacilli which elicits the allergic reaction. Zinsser (2) ascribed reactions in infected animals to a diffusible, polypeptid-like element of the protein, and Long and Seibert (3), after preparing tuberculin from a nonprotein medium, have reported that "a substance of protein nature is responsible for the tuberculin reaction," and that possibly more than one protein can elicit the reaction. The protein substance is precipitated partly but not completely by acetic, phosphoric and hydrochloric acids, and completely by three-fourth's saturation with ammonium sulphate. It is nondialyzable.

That immunity and allergy fluctuate and wane with the aging or healing of tuberculous infection is indicated by the results of protective inoculation of cattle with living human tubercle bacilli. Cutaneous hypersensitiveness and a relatively high immunity to later infection with bovine tubercle bacilli can be thus produced, but the immunity, the allergy, and the human-bacillus infection will all have largely subsided two years after the immunizing infection.

Baldwin (4), Krause (5) and others observed that, as cutaneous hypersensitiveness disappeared or became much less intense with the healing of tubercle, animals with human or bovine infection still showed some immunity; and they thought that the allergy was simply "latent," for it would reappear almost *immediately* upon reinoculation with tubercle bacilli. Gelien and Hamman (6), from clinical observations, expressed their belief in a fluctuating hypersensitiveness, with sharp rises upon reinfection (metastatic), in the course of human disease. Kraemer (7) also pointed out that there is a fluctuation of hypersensitiveness, and he emphasized that one should think of healing as being anatomical, biological or bacteriological.

The plan of the following experiment was to observe cutaneous hypersensitiveness in tuberculous guinea pigs through a relatively long period after infection, and to compare at intervals their degree of immunity to reinfection with their allergic state, as shown by the reactivity of the skin. To this end guinea pigs were first inoculated with a strain of tubercle bacillus of low virulence (R1) and, at trimonthly intervals beginning one year after infection, they were given intracutaneous tests with tuber-

culin (water-extract), and were, a few days later, inoculated subcutaneously, together with normal controls, with suspensions of virulent tubercle bacilli (H37).

INFECTION AND RESULTS OF SKIN TESTS

On November 17, 1920, thirty guinea pigs, of 300 to 500 gm., were innoculated subcutaneously in the right groin with 0.5 cc. of an emulsion of R1. Within two to three weeks of the infection all the animals had palpable lymph nodes in the right groin and certain unselected ones of them gave skin reactions to tuberculin. From this time until November

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PLATE 1

A series of representative skin tests done at intervals of one year, two years and twenty-seven months after R1 infection, together with illustrations of the type reaction in uninfected and in recently infected (R1), highly allergic guinea pigs.

Fig. 1. Reaction after intracutaneous tuberculin test in animal one year after R1 inoculation. The reaction is lively, but is not quite as vigorous as is the rule in R1 animals two or three months after infection.

Fig. 2. Area of tuberculin test in normal control. This animal received the same dose of tuberculin as the animal shown in fig. 1.

Fig. 3. Area of tuberculin test in an animal two years after R1 inoculation. The reaction is negative although twice the usual amount of tuberculin was injected.

Fig. 4. Area of tuberculin test on the same animal as shown in figure 3, but done four days after the animal was reinfected with H37. The normal animals infected for the first time with H37, as controls to the two-year R1 animals, showed no skin reaction to tuberculin at this time.

Fig. 5. Tuberculin reaction in a guinea pig twenty-seven months after R1 inoculation. A very large dose of tuberculin (five times the usual dosage) was used.

Fig. 6. Typical, vigorous reaction to tuberculin in a recently infected R1 animal (6 weeks).

15, 1921, the animals lived an ordinary cage life, thrived, and grew sleek and fat. In most of them the lymph nodes of the right groin were palpable at the end of the year; in others no nodes could be felt. Hereafter in this paper these infected animals will be referred to as *immunes*, and in each case the noninfected controls as *nonimmunes*.

Normally, the reaction to tuberculin is an inflammation, characterized by redness and induration and frequently by central haemorrhage and necrosis. Occasionally pallor or a normal color of the skin, instead of hyperaemia, is associated with induration in a reaction. The height of the reaction is usually reached within twenty-four hours and practically always within forty-eight hours after the injection of tuberculin. It is

taken as an arbitrary index of a positive reaction that the area involved should measure at least 1 cm. in its longest diameter.

One Year after Infection: On November 15, 1921, one year after the sensitizing R1 inoculation, each of five of the immunes (nos. 1 to 5) and

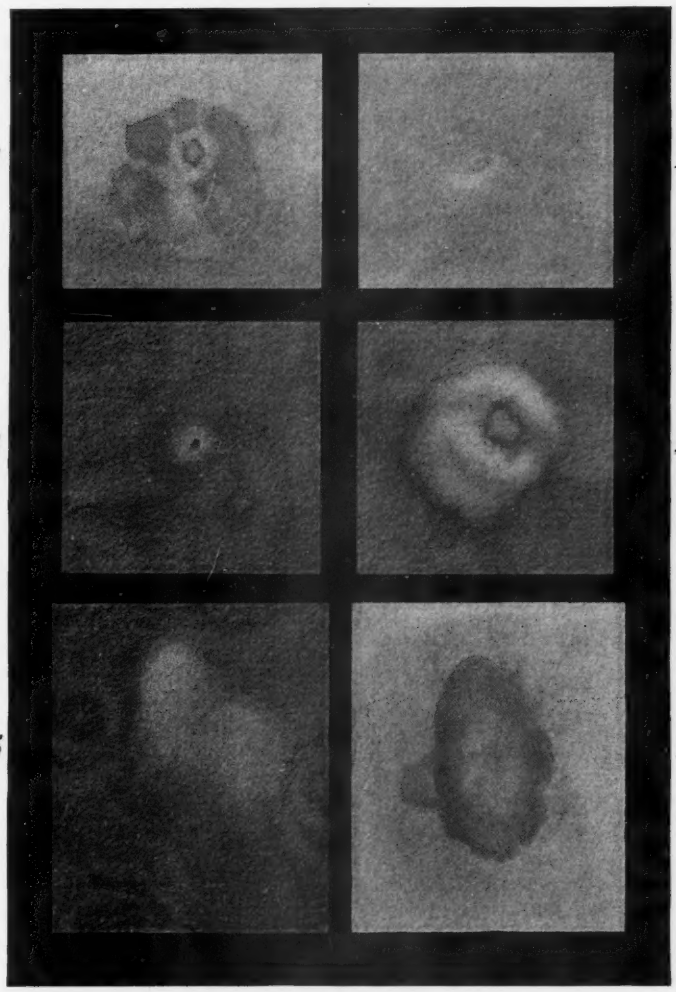

PLATE 1

each of five large nonimmunes (nos. 6 to 10) received an intracutaneous tuberculin test with W.E. 309.[2] One day later four of the immune

[2] W. E. 309 was prepared as follows: 50 gm. of pulverized H37 tubercle bacilli (medium-free) were placed in 1000 cc. of sterile distilled water and extracted at 48° to 52°C. for forty-eight

animals (nos. 1, 2, 4 and 5) each showed a definite reaction, with redness and moderate induration. Although quite definite, the reactions were not as pronounced or as large as is the rule in animals tested within a few months of their infection with R1. The reaction in one animal (no. 3) was equivocal. There were no signs of reaction in the skins of the non-immune controls. The reacting areas of the immunes were drawn in color and one of these drawings is reproduced in figure 1, which may be contrasted with figure 2, a drawing of a test-area in one of the nonimmunes. Details of the areas of reaction are given in table 1, in which, besides data of the results of the tuberculin tests, appear the autopsy findings from the inoculation of virulent tubercle bacilli in the various groups of animals, tested and infected with H37 at regular three-month intervals from one year to more than two years after the original R1 inoculation. In table 1 are given the areas, by measurement, of redness or pallor, and the degree of induration. Reference to this table will be repeatedly made.

Fifteen Months after Infection: At fifteen months after the sensitizing R1 inoculation (February 12, 1922) five other immunes (nos. 11 to 15) and five large nonimmunes (nos. 16 to 20) were each given an intracutaneous test with W.E. 309 according to the same technique used in the first group. A reacting capacity was present, but the reactions were not as vigorous or as extensive as earlier in the course of infection. No reactions were observable in the nonimmunes. These results are recorded in table 1.

Eighteen Months after Infection: Again at eighteen months following the sensitizing R1 infection (May 10, 1922) four immunes (nos. 21 to 24) and four large normals (nos. 25 to 28) were tested in the usual way. The resulting reactions in the immunes were fainter and less pronounced than any observed in the former two series, but reaction was sufficiently vigorous in one animal (no. 22) to be regarded as positive. The non-immunes were negative.

Twenty-One Months after Infection: A fourth series of four animals each, immunes and nonimmunes (nos. 29 to 32, and 33 to 36), was tested

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hours. The flask was repeatedly shaken during this period. The material was then allowed to settle in the icebox for two weeks, when the clear, straw-colored supernatant fluid was passed through a sterile Berkefeld filter, placed in bottles and preserved with a layer of toluol. One cubic centimetre upon evaporation contained 0.01275 gm. of bacillary material. For intracutaneous injections 0.1 cc. of the extract was diluted with an equal part of physiological salt solution, and a total bulk of 0.2 cc. was injected.

in the usual way at twenty-one months after the sensitizing R1 inoculation (August 14, 1922), but no animal in either group reacted noticeably. In one of the immunes (no. 32) there was a faint flush, with barely detectable induration at the site of injection of the tuberculin.

Two Years after Infection: At two years after R1 infection (November 19, 1922) a fifth series of four animals each, immunes and nonimmunes (nos. 37 to 40, and 41 to 44), was tested intracutaneously with *double* the usual dose. This increased dosage aimed to determine whether the infected animals, which had now become practically nonreacting to the customary doses of tuberculin, might react to a larger amount. It did give rise to a questionable reaction in one of the four immunes.

A few days after the last-named skin tests, the animals in both the immune and nonimmune groups were inoculated subcutaneously with virulent tubercle bacilli (H37), as had been the procedure all along in the experiment. Three days after this inoculation, intracutaneous tests with tuberculin (W. E., 0.1 cc.) were made on all eight animals. One of the immunes (no. 39) at twenty-four hours showed an area of redness, 20 × 20 mm., and a moderate degree of induration. Again at four days after the inoculation, the intracutaneous tests (W. E., 0.1 cc.) were repeated on all animals and this time all the immunes except no. 40 gave marked and characteristic reactions, whereas the nonimmunes showed no reaction whatever. That is, within four days of reinfection of previously infected animals, which had lost their cutaneous reactivity to usual doses of tuberculin, a high degree of cutaneous allergy had returned. Figure 4 shows this recovered reactivity, in the same animal as that illustrated in figure 3, which is a drawing of the area (at twenty-four hours) in which the test had been made four days previously with practically negative results.

Twenty-Seven Months after Infection: Only two untested guinea pigs remained at this time (nos. 45 and 46), but these were now tested intracutaneously with five times the ordinary dose of water-extract (0.5 cc. W. E. 309 and 0.5 cc. physiological saline solution). One animal failed to react: the other gave a reaction characterized by a diffuse and indistinct redness with ill-defined margins. The reaction is shown in figure 5. In extent it was a large reaction, but in depth of color and degree of induration it was regarded as slight or moderate. The normal controls also showed an area of transient redness at the site of injection of the large volume of material. These animals were not infected with H37, but were kept for later observation.

Thirty Months after Infection: May 17, 1923. It was desirable to use the remaining (45 and 46) guinea pigs for a final effort to ascertain the state of allergy at this long time after their infection with R1. This time their allergy was tested, not with tuberculin, but with virulent tubercle bacilli. They were therefore inoculated intravenously, each with a heavy suspension of tubercle bacilli (H37), in order to find out whether allergic reactions would develop at the focalizing sites of the newly introduced bacilli and whether a constitutional reaction would follow the inoculation. One animal (no. 46) received 0.25 cc. and the other (no. 45) 0.1 cc. of the suspension. Two normal animals and one *recently* infected with R1 (and therefore presumably highly allergic) were similarly inoculated with 0.1 cc. of the suspension at the same time. Twenty-four hours afterward the recently infected R1 control was moribund, but none of the other four showed any signs of illness or discomfort. One of the two normals, the ill R1 control and immune no. 46, were killed. The R1 control showed a large number of 3- to 5-mm. grayish-brown spots of apparent consolidation and innumerable pinpoint, whitish, opaque areas scattered widely over the surface of both lungs. The spleen was large and very wet. The normal control and no. 46 presented lungs and other viscera of normal appearance. On the eighth day after virulent inoculation immune no. 45 and the second normal control were killed. No. 45 showed an enlarged, soft, and very wet and inflamed spleen, and lungs which were "peppered" with large numbers of minute tubercles, much better seen after zenker-fixation. The liver was also full of pinpoint areas resembling tubercles. In the normal control the spleen had magnified malpighian bodies, and the liver a few just visible whitish areas, but the lungs appeared perfectly normal.

It is not safe to draw conclusions from such small numbers of animals, but the impression one gets is that, although there was not a sufficient degree of allergy in these remaining animals to produce a profound reaction such as occurred in the R1 sensitized control, there was in one of the two immunes (no. 45) enough to produce the rapid reaction and early tubercle-formation characteristic of hypersensitive and immune animals. The animal (no. 45) which showed early tubercle-formation

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Table 1. Data concerning intracutaneous tuberculin tests, inoculations and autopsies of animals. The time-interval between original sensitizing (R1) inoculation and reinoculation and the results of the intracutaneous tests and the autopsies in the several groups are given. The matter receives analysis in the text.

Number of Animal		Date of Intradermo Test	Tuberculin	Skinreaction 24 hours		48 hours		Date of H37 inoculation	Time between R1 & Horinoc.	Date of Autopsy	Autopsy findings					
Immune	Nor. Immune			Redness	Induration	Redness	Induration				Pr. groin	L. groin	Spleen	Liver	Lungs	Tr. Br. Nodes
1		Nov. 15th 1921	1 year	15×15 mm	+	15×15 mm	+	Nov. 21st 1921	1 year	Febr. 19th 1922	0	++++	0	0	0	++++
2				25×30	++	20×30	+				+	+++		0	+	++++
3				?	?	0	0				0	+++	?	0	+	+++
4				15×15	+	15×15	+				+	++	0	0	?	++
5				slight	+	0	+				+++	+++	+	0	?	++
	6			0	0	0	0					++++	++++	++	+++	++++
	7			0	0	0	0					++++	++	+++	+++	++++
	8			0	0	0	0					++++	++++	++	+++	++
	9			0	0	0	0					+++	++++	++++	++++	++++
	10			0	0	0	0					++++	++++	++++	++++	++++
11		Febr. 12th 1922	15 months	slight	slight	10×10	+	Febr. 17th 1922	15 months	May 12th 1922	Normal	++	+	0	++	++
12				„	„	12×12	++				+	+++	++	0	?	+++
13				„	„	12×20	++				++	+++	++	0	+	++++
14				„	„	6×10	+				++	++	0	0	?	++++
15				„	„	0	0				Normal	++	0	0	+	++++
	16			0	0	0	0					+++	+++	++	+++	++++
	17			0	0	0	0					++++	++++	+	++++	++
	18			0	0	0	0					++	+++	0	+++	+++
	19			0	0	0	0					+++	++	0	+++	+++
	20			0	0	0	0					+++	++++	++++	++++	++
21		May 10th 1922	18 months	faint blush	0	0	0	May 17th 1922	18 months	Aug. 14th 1922	+ very slight	+++	++	0	+	+++
22				„	0	10×10	+				„	+++	+	0	++	++
23				„	0	5×7	+ (sl.)				Died 6 days after H37 inoc.					
24				0	0	0	0				0	+++	+	0	++	+++
	25			0	0	0	0					+++	+++	++++	+++	+++
	26			0	0	0	0					++	++	+++	++	++
	27			0	0	0	0					++++	++++	++++	+++	++++
	28			0	0	0	0					++++	++++	0	++++	++++
29		Aug. 14th 1922	21 months	0	0	0	0	Aug. 15th 1922	21 months	Oct. 13th 1922	0	+++	0	0	++	0
30				0	0	0	0				+	+++	+	0	+?	++
31				0	0	0	0				+ very slight	++	+	0	+	++
32				faint flush	0	faint flush	0				0	++	?	0	+	+
	33			0	0	0	0					++++	+++	++	++++	+
	34			0	0	0	0					++	+++	++++	++++	+
	35			0	0	0	0					+++	+++	++++	++++	+++
	36			0	0	0	0					+++	++++	++++	+?	+
37		Nov. 19th 1922 **	2 years	v. faint blush 5×5	0	v. faint 5×5	0	Dec. 9th 1922	2 years	Febr. 5th 1923	0	++	+	?	+	++
38				0	0	0	0				+	+++	+?	0	?	++
39				0	0	0	0				++	++	+	0	+	+
40				faint blush	0	0	0				+	++++	0	0	?	+
	41			0	0	0	0					++++	++++	+++	+++	++++
	42			0	0	0	0					++++	+++	+++	++	++++
	43			0	0	0	0					++++	++++	++++	+++	++
	44			0	0	0	0				Died too early for infection					
45		March 8th 1923 ***	27½ months	faint marked 25×30	++	faint diffuse 25×30	++									
46				slight 20×20	+?	slight 10×10	0									
	47			slight 20×30	+?	7×10	0									
	48			slight 20×30	+?	0	0									

* Not definitely tuberculous
** Double the usual amount of W.E. used
*** № 45 given 1.0 cc solution
. 46 „ 0.75 „ „

TABLE 1

was the same one which gave a reaction three months before to a very large injection of tuberculin in the skin. The other one failed to react allergically to tuberculin.

RESULTS OF INFECTION OF THE TWO GROUPS

The next step was to compare the degree of hypersensitiveness, as shown by the allergic state of the skin, with the degree of immunity to reinfection of the same animals with virulent tubercle bacilli. Accordingly, as has already been stated, at each three-month period, and a few days after the tuberculin skin-tests were made, each animal of the group, along with controls, was inoculated subcutaneously in the left groin with a suspension of virulent H37. Eight to twelve weeks later the animals were killed, and the amount of disease in the individual animals of the immune and nonimmune groups compared. The findings at autopsy are charted by organs in table 1, where the relative extent of involvement in each organ or tissue is represented by + to ++++, + indicating definite evidence of disease although there may have been only one single area of tuberculosis, and ++++ indicating very extensive disease. It will be seen that in every lot the nonimmunes fared definitely and decidedly worse than the immunes. The immunes which gave no skin reactions, as well as those which did react, showed no appreciable difference in their resistance, which, in both, was high, and much above normal. The immunes with good cutaneous hypersensitiveness, infected with H37 one year, and those with a disappearance of cutaneous hypersensitiveness, infected with H37 two years after R1 inoculation, presented no differences. By further reference to the table it will be seen that the spleens, for instance, in the various groups of immunes, showed remarkably little involvement throughout and but slight differences between the first and last groups; yet these organs in the groups of nonimmunes showed marked tuberculosis. Of the livers of the immunes, none showed disease in any group; in the nonimmunes there was considerable hepatic tuberculosis. The lungs of the immunes showed, as a rule, slight but fairly constant involvement. The ratio of involvement of the lungs of the immunes to that of the nonimmunes was a little greater than 1 to 4 (1 to 3.5). The tracheobronchial lymph nodes were more nearly alike in the two groups, but comparison here may not necessarily be of very great significance, because R1 may nest in these nodes for a long time, and one could not be certain as to how much the original R1

infection contributed to the enlargement of these structures in the immunes.

SUMMARY

The above experiments contribute nothing new in principle to the known effects that retrogressing (sclerosing, healing) tubercle may have on the tissue hypersensitiveness that results from tuberculous infection. They show, as has long been established (5) and generally accepted, that allergy fluctuates with the course of infection; and, particularly, that as infection subsides or heals allergy diminishes. Indeed, after two years this diminution had proceeded to the point of virtual disappearance of the hypersensitive state; as, for instance, in the animal shown in figure 3, in which twice the ordinary reacting dose of antigen failed to elicit a response.

Yet, as concerns tuberculo-allergy, once it is established and for as long as its basis (anatomical tubercle) persists, such commonly used terms as *disappearance*, *inhibited*, etc., must possess in reality only a relative significance. The terms may adequately characterize the results of tests with the ordinary dose of tuberculin, and be accurate enough in practice and for purposes of practice; a "two-year" animal is negative to 0.1 cc. of tuberculin (W.E.) and even twice this standard dose, and might go down in the record as with "allergy lost." But at twenty-seven months *five* times the standard dose does bring out undeniable evidences of hypersensitiveness in an animal.

The case is not dissimilar in man. The classical examples of so called "lost" or "disappeared" or "inhibited" allergy in the presence of tuberculous infection in man are, according to various writers, to be found in fulminating or terminal tuberculosis, that condition in which reacting power is either overwhelmed or spent. Yet when this dictum was put to the test by Happ and Casparis (8), the authors found that any and every tuberculous person, the dying "meningitic," or the child at the end of miliary generalization, would react allergically if subjected to enough tuberculin.

But, though we may suppose that in our experimental animals some allergy remained after infection had receded to almost the vanishing point, there can be no supposition as to the very great reduction of allergy in the circumstances, and, too, as to a high and competent degree of immunity existing under these conditions,—that is, with infection all but healed and allergy barely demonstrable.

It is these relations of immunity that are difficult to square with current ideas of the place that infection and allergy occupy in the mechanism of tuberculoimmunity. Krause, for instance, hypothetically puts forward immunity as being a function of allergy (9). He has frequently pointed out how the two phenomena (immunity and hypersensitiveness) keep step at all known points, as summarized at the beginning of this paper. Accordingly, one would expect, in animals with healing or healed tubercle and with allergy low or hardly detectable, to find a much reduced immunity, if, indeed, it were to be discerned at all.

Any attempt to account for the discrepancy (according to Krause's hypothesis) between the coexistence of a high immunity and a low or apparently absent allergy will no doubt be obliged to take into account much more complicated factors than superficially appear. And decisively important will be the central question as to whether tuberculoimmunity must be conceived of as a property that is always "active" as long as it is in existence. May not specific immunity to tuberculosis become "latent" a long time after infection? Or is immunity a state of delicate balance, which may very quickly be transformed from a state of latency or of low immunity to one of high immunity? We are told that such a condition may exist in immunity to typhoid fever, in which a person after recovery from the disease, or after inoculation of the typhovaccine, may not necessarily give a positive agglutination test under ordinary circumstances, yet exhibit a good Widal reaction almost immediately after a new introduction of typhoid bacilli or vaccine into the body (Wollstein (10)).[3]

The failure of the skin to react positively to the doses of tuberculin usually administered in experiment is not necessarily proof of an entire absence of allergy. Two facts indicate this: (1) the successful demonstration of allergy by the use of larger amounts of tuberculin, and (2) as can be easily demonstrated, after a new reinfection, the very prompt return of an allergy that the ordinary doses of tuberculin had failed to evoke before the new reinfection. It will be remembered that some of the animals that were negative to the customary dose of W. E. reacted to larger doses, and that when old R1 animals, in which no skin test was elicited by the usual doses of tuberculin, were reinfected with H37 and then retested, they gave marked and typical reactions to the same doses

[3]This is simply regarded as a parallel, however, and does not seek to confuse a consideration of immunity to tuberculosis by discussing agglutinins and immune bodies.

of tuberculin that had been used without reaction four days previously. Four days is, of course, entirely too short a time for allergy to become initiated in a previously normal animal. In other words, the new infection with H37 "whipped up" to new levels an allergy that had sunk to a scarcely detectable point with the healing of the old process,—another example of the general immunological law of accelerated and heightened response of "immune bodies" to fresh applications of antigen.

If allergy becomes "latent," its capacity for being "whipped up" so promptly after reinfection may carry an explanation of the high immunity that was found in these animals in the presence of a fading allergy. For all we know to the contrary, the immunity may also be "latent" and may be immediately stimulated to a high functioning level by the fresh infection at the same time that allergy is demonstrably restored. There is so much other good evidence that the two phenomena coexist in a functional interrelation that it is allowable to suppose that both might be restored together to old high levels.

CONCLUSIONS

1. After infection with tubercle bacilli of low virulence, guinea pigs exhibit a gradually declining cutaneous allergy as the infection subsides.

2. At two years after infection they failed to react to twice the usual reactive dose of tuberculin.

3. At twenty-seven months after infection one animal reacted positively to five times the ordinary reactive dose of tuberculin.

4. Notwithstanding this greatly reduced and practically absent allergy, such guinea pigs, at thirty months after infection, were found to possess a high specific immunity to reinfection with virulent tubercle bacilli.

5. The relations between tuberculoimmunity and tuberculoallergy are discussed.

6. Particularly discussed is the question of possible latency of either allergy or immunity, or of both, and the probable effect of reinfection on such latency.

7. It is shown that a scarcely detectable allergy in old and healing infection is *immediately* restored to old high levels by fresh reinfection.

8. It is suggested that reinfection may similarly revive a waning tuberculoimmunity.

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THE PULMONARY EFFECT OF OVER THREE YEARS' EXPOSURE OF GUINEA PIGS TO SILICA DUST[1]

HENRY STUART WILLIS

An investigation into the effects of the inhalation of dusts upon the anatomy and physiology of the lungs, especially of the pulmonary lymphatics, of experimental animals, and the influence, if any, of these changes upon subsequent infection of these animals with tuberculosis has been going on for several years in this laboratory, and the earlier results of the study have been presented in two papers (1) (2). In the first of these there was discussed the general proposition that, through its anatomical effect on the lymphatics and lymphoid tissue of the lungs, the inhalation of dust might so alter the physiology of these organs as to modify their response to tuberculous infection, for it is well known clinically that prolonged inhalation of certain dusts will produce anatomical changes in the lungs which may manifest themselves symptomatically or may modify the susceptibility of the lungs toward the superimposition of infectious disease. That study presented the prevailing views as to what are the harmful types of dust and what are the results of their inhalation, and showed the changes that occur in the lungs of nontuberculous guinea pigs that are kept sufficiently long to develop spontaneous pneumonokonosis. The second paper described the effects on guinea pigs of experimentally inhaled coal dust and the results, in turn, developing from tuberculosis when induced in animals so exposed.

It is well known that not all dusts produce like effects in the lungs. Many investigators, on apparently good evidence, believe that the softer dusts, such as coal or cement, not only do not produce deleterious effects upon the lungs, but even confer a protection, in so far as the likelihood of subsequent development of pulmonary tuberculosis is concerned. But there are important contributors who take issue with this position. Important evidence likewise supports the view that the harder, more crystalline dusts, silica especially, do great harm to the lungs.

[1] From the Kenneth Dows Tuberculosis Research Fund of the Johns Hopkins University and Hospital, Baltimore, Maryland.

This paper is a report of still further study on the general question of the relation of the experimental inhalation of dust to pulmonary tuberculosis. It deals specifically with the effects of very prolonged inhalation of a hard dust: first, with the effects on the lungs and, second, with the influence of these effects upon the course of the infection in such animals after inoculation with tubercle bacilli. It was desirable to know (1) whether very long exposures of two or three years to dust would produce in animals pulmonary changes that might be comparable to those found in human beings in the dusty trades; (2) whether, under similar conditions of exposure to dust, the animals which inhaled hard dusts would develop more marked signs of pulmonary damage than those exposed a corresponding length of time to coal dust; and (3) whether tuberculous infection induced in guinea pigs that had had long exposures to hard dust would differ from similar infection in normal animals or in those exposed to a soft dust, such as coal. The animals of this experiment were probably given longer exposures to dust than any previously reported by any author.

Before entering into a consideration of the actual details and results of the study, it is germane to comment briefly upon the literature on the relation between dust inhalation and tuberculosis and the influence of the former upon this infection, for several points of view have been presented. The salient features in the literature concerning pneumonokoniosis itself have been given (1) (2) and need not be repeated.

One group of workers has presented the claim that the changes set up in the lungs by dust inhalation definitely predispose to pulmonary tuberculosis. Ramazzini (3) was among the first to observe a relation between dusty work and consumption and the first to publish a book on the subject. He wrote in 1705 in his chapter on the diseases of stone cutters: "They oftentimes suck in, in inspiration, the sharp, rough, and corner'd small splinters or particles that flie off; so that they are usually troubled with a cough, and some of 'em turn asthmatick or consumptive." During the same century the prevalence of consumption was noted among quarrymen (Coschewitz (4)), grinders (Simmons (5)), marble- and plaster-workers (Desgenettes (6)), needle-factory employees (Johnstone (7)), stone-cutters and other workers (Beddoes (8)). Recently Middleton (9) has reported that silicosis definitely lays one liable to develop tuberculosis and just as definitely hastens the process to a fatal issue, once it is developed. And this opinion has also been held by Collis (10), Oliver (11), Lanza (12), Watt, Irvine, Johnson and Stewart (13), Arlidge (14) and others, from clinical observation.

One of several experimenters, Cesa-Bianchi (15), exposed infected guinea pigs to various dusts; they developed pulmonary tuberculosis with extensive cavitation, while his control animals showed little pulmonary disease. Ascher (16) infected rabbits with bovine tubercle bacilli, and exposed them to smoke, and concluded that the exposed animals were more prone to the development of pulmonary tuberculosis, and more prone to have the process accelerated. Gardner's (17) conclusions, that more tubercle occurs in the lungs of animals exposed to the inhalation of granite dust than in the lungs of undusted animals, and that (18) a more extensive and more chronic tuberculosis follows infection in those that have inhaled carborundum, support the contention of this group of workers.

Another group of authors purports to show that phthisis, as such, is not wholly responsible for the high mortality from tuberculosis among workers in dust. Landis (19), for instance, held that the great danger from dust-particles lay in their capacity to carry tubercle bacilli with them when inhaled, and he believed that the general hygienic and economic surroundings of workers in dust are matters of more importance in producing pulmonary disease than is the inhalation of dust *per se*. In the opinion of Watkins-Pitchford (20), tubercle bacilli may be found in a very high percentage of silicotic lungs in the late stages of the disease when necrosis is present, but there are very often slight or no histological evidences of tuberculous reactions: the bacilli encountered under these circumstances are to be regarded as saprophytes. But Watkins-Pitchford was convinced that histopathological evidence of tuberculosis points to a tuberculous complication of the silicosis, for the silicotic lung in all stages is more liable than the normal to tuberculous infection. This author believed, however, that the general insanitary conditions in the mines account for a great deal of tuberculosis among the workers. Upon examining 250 specimens of expectoration taken at random from the floor inside the mines, he (21) found that 15.2 per cent contained tubercle bacilli, while only 2.5 per cent of 120 specimens from the surface outside the mines contained bacilli. Lanza found a great deal of tuberculosis in the very bad hygienic surroundings of the homes of the zinc-miners he investigated. Goldmann (22) reported an actually higher mortality from tuberculosis among coal-miners' families than among the miners themselves.

A third group of authors attempts to show that certain dusts (mostly coal) actually act as a preventive against the development of pulmonary tuberculosis, but this possibility has already been commented upon briefly in our *Study IX* (2).

TECHNIQUE

The procedures employed resembled very closely those described for our studies on coal dust.

Apparatus: A description of the dusting apparatus, together with an illustration of it will be found in *Study IX*, to which the reader is referred. In this experiment exposures were carried out with the dust-box mentioned in *Study IX*, with the important exception that a modification of the dust intake provided for a small though continuous delivery of dust to the rotating sieve and thus ensured a continuous supply in the chamber.

Concentration of Dust: When the dust was delivered to the rotating sieve the latter sifted it very promptly, allowing it to fall on to a rotating fan, which spread it uniformly throughout the box. An analysis[2] of the air in the box was made during the height of the dusting process; a second analysis was made at ten and another at twenty-five minutes after the machinery had ceased running. These intervals represented concentrations of the dust as they occurred several times during a given exposure, for, as a rule, a supply of dust was placed in the funnel at the top of the box and the funnel was allowed to empty itself completely before a new supply, usually an amount sufficient to require about one-half hour for emptying, was added. This was done to facilitate complete emptying and to prevent clogging of the apparatus, which occasionally happened unless this precaution was employed. At each exposure the animals were allowed to remain in the box one-half hour after the box had ceased to function, and this was an added reason for determining the content of the air during this period. The average concentrations of particles smaller than 10 micra in diameter were as follows:

During the active feeding-in of dust	675,000,000 per cubic foot
Ten minutes after cessation of dusting	19,000,000 per cubic foot
Twenty-five minutes after cessation of dusting	4,590,000 per cubic foot

Within three or four minutes of the discontinuance of the dusting, the cloud of dust, which never appeared more than a moderately thick haze, disappeared, but the count of particles remained very high even at twenty-five minutes, and was almost unbelievably high at the height of the dusting.

Dust: The dust used bears the trade name of *Crystolon*[3] which is an artificial abrasive produced by fusing a mixture of sand, coke, sawdust and salt in an electric furnace. Upon analysis, an average sample was found to contain:

Carbon	0.25	
Silica	0.50	
R_2O_3	1.25	ferric and aluminum oxide
Silicon carbide	98.00	

[2] These counts were made through the good offices of the United States Public Health Service and the kindness of Mr. J. J. Bloomfield, representative of the Service.

[3] It has been very generously supplied by the Norton Company, Worcester, Mass., who manufacture it and who provided the analysis given above.

It is a very fine, almost impalpable, powder of slate color, that may be readily suspended in a cloud in the air. Under the microscope the particles appear as very small crystalline or angular bodies, refractile and lying for the most part together to form small, opaque, amorphous masses but often singly and having a faintly greenish color. Figure 1, a retouched photomicrograph of a preparation of the dust, shows several of its characteristics. The slide on which this

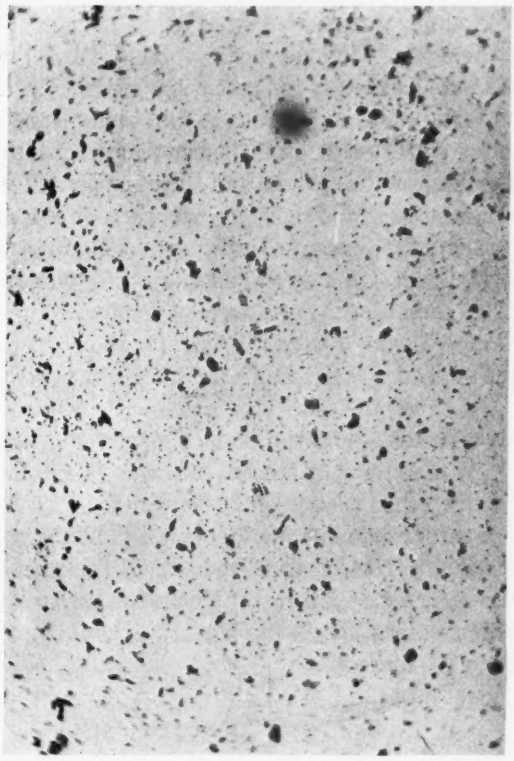

FIG. 1. PHOTOMICROGRAPH OF SLIDE EXPOSED IN DUST-BOX FOR ONE-HALF MINUTE

sample was collected was smeared with a thin layer of egg-albumin and allowed to remain one-half minute in the dust-box.

Exposures: Exposures averaged about three hours a day for four or five days a week, although at certain periods the exposures of some of the animals were more intense. In general the animals may be said to have been in the dust-box about fifty hours a month. Under this regimen, one group of animals spent over three years (thirty-seven months), and another group over two years (twenty-eight months). The animals were given a week's rest from the dust-chamber about every two months.

Animals: Seventy-five guinea pigs were used in the experiment before infection: after this 20 were added as normal controls. Guinea pigs were used exclusively, just as in the study with coal dust, because experimental tuberculosis normally involves the lungs to but a slight extent and thus differences, if any, would be more easily detectable. In these animals the lungs normally possess but a small amount of lymphoid tissue, and any appreciable increase or alteration of this tissue would be more easily detectable than if it had taken place in a lung containing a large amount of it.

Infection: At the end of the long dusting period, 18 of the 75 animals remained, some of them, as already indicated, having been in the experiment a little longer than three years, and the others for twenty-eight months. These 18 animals, together with 10 old normal guinea pigs, known to be of the same age as those of the three-year exposure, and 10 young normal guinea pigs were inoculated subcutaneously in the right groin, each with 0.1 cc. of a comparatively thin suspension of the commonly used strain of human tubercle bacilli of moderately high virulence, H37. One-half of all these guinea pigs were killed six weeks, and the others eleven weeks after infection.

Fixation and Preparation of Tissues: Except for an occasional specimen that was either cleared or fixed in Kaiserling's fluid, the tissues were preserved with Zenker's fluid. At times the fluid was introduced intratracheally with the lungs intact, but as a rule the latter were removed and looked at carefully before fixation. In these circumstances, care was taken not to distend the lung abnormally during the injection of the fixing fluid into the trachea. When occasionally a mesenteric lymph node was enlarged or discolored, it was also fixed in Zenker's fluid. Nearly all of the tissues designed for section were selected, cut from the lung with a razor, blocked in paraffin and cut in serial sections. A few were cut from celloidin blocks. The thickness of the sections ranged from five to 200 micra.

INDUCED PNEUMONOKONIOSIS

During the long period of exposure a good many of the animals died, the mortality being much greater than that in animals of equal age that were being kept for controls. This was true despite the fact that every care was taken as to the cleanliness of their surroundings, abundance of diet and general attention. During the first year 12 animals died, during the second year another 12, and during the third 23. This does not include seven that died acutely within a short time from a "purulent pneumonia."[4] The lungs and mesenteric lymph nodes of all these

[4] The causes of the high mortality among these animals, aside from these seven, varied a good deal, but pneumonia caused many more deaths than any other single disease, 30

animals were preserved. Careful descriptions of the fresh tissues were made and sections of a large number of representative specimens were cut and studied. Most of the deaths occurred from causes that appeared to affect little, if any, the distribution of dust in the lung, and it is upon a study of these tissues that a good part of the description of the anatomical reaction of the lung to dust rests.

Gross Changes in Lungs and Pleura: Gross changes did not appear until after several months of dusting. After four or five months the lungs became marked with occasional indistinct, hazy, grayish-white areas, poorly set off from the tissue, and scattered rather widely over the surface but tending to be more numerous in the dependent portions of the middle and cephalic lobes. At this time these areas sometimes had reached a diameter of 1 or even 2 mm., and the entire lung was occasionally overcast with a diffuse, very faint, grayish discoloration. The patches of dust tended to become more sharply defined as the duration of exposure increased, and from eight months to a year and a half they were, in general, more numerous, and often connected by a tracery of lines of irregular thickness, that varied from a just perceptible width to 1 mm., the lines often being of a granular character and beaded irregularly as they connected the several spots.

The change from normal to pigmented lungs developed so gradually and (frequently) so inconstantly as to be unappreciable from month to month. Still later in the course of the exposure, when animals had been in the dust-box for as long as three years, the lungs in general showed a larger number of pigmented points, and these tended usually to be larger and more sharply defined than those of the shorter periods of dusting. In these animals, too, the connecting lines were as a rule better developed,

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per cent of the animals dying from it. This, however, tended to be sporadic rather than epidemic, for it was only occasionally that an animal died, and contact with the sick seemed not necessarily to subject others in the same cage to a like disease. As a rule, too, the pneumonic process was not very extensive, usually being distributed as patches in one or several lobes, and occasionally involving a lobe and rarely more than one. Several animals died of a pus-forming infection of the pleura or pericardium and sometimes of the peritoneum, with abscesses in the lungs or liver that contained small gram-positive cocci. A few became in very poor condition, and developed cutaneous inflammation, abscesses and ulceration over the back and rump from fighting, and died. A very few, especially older ones, died from an infection (*Streptococcus haemolyticus*) of the cervical lymph nodes, which became connected with very large abscesses of 2.5 to 3 cm. in diameter. Several at autopsy appeared normal.

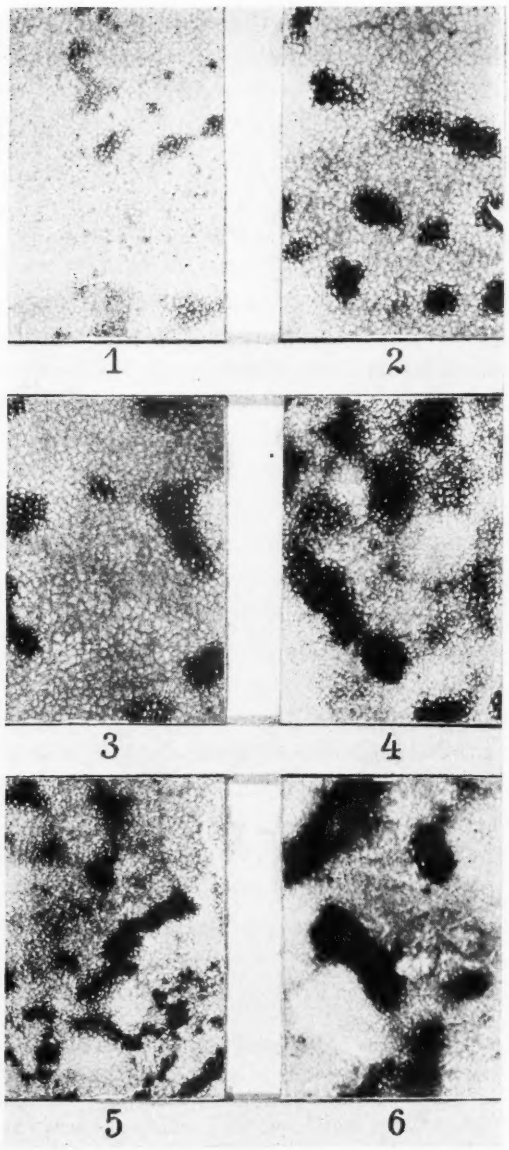

FIG. 2. PHOTOGRAPHS OF THIN SLABS OF PLEURA AND A LITTLE UNDERLYING TISSUE FROM ANIMALS OF VARIOUS PERIODS OF EXPOSURE

1: 10 months. *2:* 16 months. *3:* 21 months. *4:* 2 years, 9 months. *5:* 3 years, 1 month. *6:* Normal, nondusted control, 3 years and 1 month in animal room.

The tissues were cleared by the Spalteholz method. Detailed description is given in the text.

and very frequently they bore a striking resemblance to the network that is so characteristic of the lungs of urban-dwelling human beings. They would connect numerous dots, to form, usually rather incompletely, squares, diamonds, irregular polygons, etc., in widely scattered regions throughout the surface of the lung. Both grossly and microscopically these looked so much like the deposits of dust in old normal, undusted animals as to seem identical with the latter, which were often even more marked than the deposits in the lungs of artificially dusted animals after prolonged exposure. This is the type picture; yet not infrequently an animal exposed for two years or even longer would at autopsy have lungs without any visible dust. This seems surprising; but it is probably not to be wondered at when one considers how tortuous and elaborate is the conformation of the upper respiratory tract in rodents and several other species of animals, including many that run with nose to the ground, sniffing and undoubtedly breathing much dust but exhibiting lungs with normal pink color, nevertheless.

In figure 2 are shown several specimens of pleura of animals that had different periods of exposure. It exhibits both the distribution of the dust and its extent. The thin slices of pleura were cut with a razor, cleared by benzene and oil of wintergreen (Spalteholz method), mounted, and photographed. It will be seen that the dust gradually becomes more abundant with increasing exposure, and that it tends to be laid down in dots and irregular, incomplete lines. In some of the preparations the individual alveoli are outlined plainly because of the dust contained in the alveolar walls. The lungs of the normal control, which had spontaneous pneumonokoniosis and was of the same age as the thirty-seven months' artificially exposed animal, actually contain more dust than those of the average animal experimentally exposed for this period. The probable reason for this is discussed later.

Another feature, that occasionally appeared in the gross examination of the lungs after long exposures, was a moderate thickening of the bronchial and vascular walls. This will also be considered later.

Not infrequently small, delicate adhesions bound the lung to the chest-wall in the animals of the longer exposures; occasionally these were numerous and firm, but they seldom appeared to have any relation to the subpleural dust deposits. They were often interlobar. They were not related to pneumonia or any other obvious infection. In a few instances the lungs were widely adherent to the diaphragm and parietal

pleura, as is shown from the following note made at the death of one of the animals:

The animal was moribund and markedly dyspnoeic: killed. Two years, seven months of exposure. The lungs collapsed but little when the diaphragm was cut away. Left epicardial lobe quite distended, and decidedly emphysematous, with numerous subpleural blebs of air 1 mm. and larger. The diaphragm adheres to both caudal lobes, firmly so on the right; both these lobes are firmly bound over their entire surfaces to the chest-wall. They feel moderately firm but not like consolidation. A pneumonic process involves the left middle and cephalic lobes, but these are not adherent except along the caudal rim of the middle lobe. These do not distend when fixing fluid is put into the trachea. They contain a few very small spots of dust. The right cephalic lobe is tied loosely to the wall of the chest by many, literally dozens, of fine fibrinous strands. It cannot be determined whether these connect with the lung at the situations of the numerous large spots and thick irregular lines of dust. Certainly some of them do not.

However, this represented the most marked case encountered.

Gross Changes in Tracheobronchial Lymph Nodes: Gradually the tracheobronchial lymph nodes became slightly discolored with gray, which, as time passed, shaded into a faint bluish-black after the longest exposures. They also quite gradually underwent a moderate enlargement, but neither this nor the pigmentation became more conspicuous than that seen frequently in old guinea pigs with spontaneous pneumonokoniosis.

Microscopic Changes in the Lungs: In *Studies VIII* and *IX* it was rather surprising to find how very slight was the reaction to the inhalation of the dust in question and how slow was the response in its evolution. We supposed that this would be more extensive and of earlier development when hard dusts were inhaled.[5] At least, this supposition is justified by clinical observations. However, the pulmonary changes in the animals of this experiment have also been very slow and very slight. Very soon after exposure, dust had become widely distributed in all parts of the lung. Practically all of it was intracellular, some of the cells containing one or two particles while many cells were filled with them. At the end of a year's exposure, and in numerous instances within a much

[5] Gardner (18) has presented the prevailing point of view as to the relative rôle of the physical (hardness, etc.) and chemical (solubility, irritating capacity, etc.) properties, and for a lucid discussion of this the reader is referred to his paper.

shorter time than this, the dust cells appeared chiefly in the following situations: (1) in the alveoli, (2) just behind the alveolar walls, (3) occasionally in the alveolar walls, (4) in the walls of bronchi, especially the smaller ones, (5) in the collections of lymphoid tissue situated at or near dividing points of bronchi and arteries, and (6) in small patches just under the pleura. Dust was present in masses of lymphoid tissue which frequently, though by no means always, appeared larger than normal, as if there had been some hyperplasia of the cells. In the bronchial adventitia a few dust-bearing cells could be seen along the lymphatics, some of them flattened out as though they might conceivably be a part of the lymphatic endothelium. A few specimens gave evidence of some thickening of the adventitia of the bronchi and especially of the arteries, but as a rule this was not marked.

After exposures that were continued for as long as three years the pulmonary changes differed in no material way from those just described, except in two respects. These were (1) occasionally a slight but measurable thickening of the walls of the bronchi, arteries and veins, and (2) occasionally an hypertrophy of the mucosal and alveolar epithelium. Among the animals that showed thickening of the trunks, the arterial *muscularis* was moderately constricted, with the result that the adventitia presented the appearance of a loosely woven basketry of connective tissue, containing wide-open and, usually, empty lymphatics and occasional particles of dust. The thickening of the bronchial walls was due more to cellular infiltration than to fibrosis. The walls of the veins were moderately thick with the same loose arrangement of fibres that characterized the arteries. All three of these structures showed a somewhat larger amount of fibrous tissue than normal when stained by the Van Gieson method. It must be emphasized, however, that this reaction occurred only occasionally, and that it was not the rule to find it.

The other feature mentioned above, namely, proliferation of alveolar epithelium and bronchial mucosa, was observed to such an extent as to become the subject of a paper to appear subsequently (25). The proliferation occurred in the bronchial mucosa and especially in the epithelium of alveoli which abut against bronchioles. At times it took on the appearance of malignant tumor formation.

Hyperplasia of the intrapulmonary lymphoid tissue in guinea pigs exposed to the inhalation of dust has been observed by Gardner (17) and other authors. It was one of the conspicuous features observed both in old guinea pigs with spontaneous pneumonokoniosis (*Study VIII*)

and in guinea pigs exposed to the inhalation of coal dust for one year (*Study IX*). It was a matter of surprise, therefore, when the intrapulmonary lymphoid tissue of the animals in the present experiment was found to be only moderately hyperplastic. This tissue in the animals subjected to 37 months of exposure resembled closely that in old animals with spontaneous pneumonokoniosis. Most of the masses of this tissue contained small collections of dust.

In the animals of long exposure the dust-cells in the subpleural patches filled more or less completely several alveoli and alveolar walls in the region, and the general appearance was quite like that seen in spontaneous pneumonokoniosis and illustrated in *Study VIII* (1). The patches represent cross-section views of the spots and lines of pigment seen grossly. When present in noticeable quantity, the dust was often more evident in the adventitia of bronchi of the third or fourth order than in the larger air-passages near the hilum. The widely distributed dust appeared no more abundant after three years of dusting than after one, but there was a good deal of individual variation: some animals showed very little dust while others showed considerable in all the situations in which dust is generally deposited. No sign of pulmonary fibrosis could be found.

By and large, the relative paucity of dust and the slightness of tissue reaction were conspicuous and surprising. The resemblance to pulmonary changes in old, normal animals throughout every aspect of the experimental findings has been very striking.

Microscopic Changes in the Tracheobronchial Nodes: There was a gradual accumulation of dust in these structures, and deposits were most commonly found in the vicinity of blood-vessels. In general, the medullary portion contained more dust, and the tendency to deposition at points between the germinal centres observed in normal animals was not apparent. Of many examinations with several different stains, among them VanGieson's, it was seldom that any sign whatever of fibrosis could be found and, when occasionally found, it was present only in the smallest amount.

RESULTS OF TUBERCULOUS INFECTION

There is both clinical and experimental evidence that the course of pulmonary tuberculosis is unfavorably influenced by the inhalation of certain dusts, especially the harder ones. The dust used in this experi-

ment was a hard dust, the chemical formula of which is known, although but little is known of its chemical action in the tissues, and we supposed that it would act upon the tissues like silica, carborundum or other such dusts. After infection, the exposures to dusting were discontinued, and the animals were divided, so that some of them were killed at six weeks after infection, in order to determine whether there would be an earlier or a more extensive focalization of disease than normal in the lungs of the dusted animals, while the remainder were killed at eleven weeks after infection, at a time before the accumulation of infection in the lungs, that ordinarily occurs late in the disease, would tend to obscure differences between the normal and dusted groups. Unfortunately, there was an insufficient number of animals to allow any to live long enough to ascertain something as to the possible chronicity of the disease in the dusted group, such as Gardner (18) has reported in the lungs of animals exposed to carborundum dust.

Differences in the animals at six as well as at eleven weeks after infection were as a rule so slight as to be negligible, except that in all the groups there tended to be rather more disease later. Therefore the results at autopsy at both times will be considered together. A count of the foci of tubercle on all surfaces of the lungs of all the animals, including the old and the young normal controls, gave an average of 37 tubercles per lung in the normals and 47 per lung in the dusted ones. But individual variations in both groups were such as to cause one to feel that this alone may not be a very dependable criterion on which to base a conclusion. The numerical increase in the dusted animals was less than that observed in animals exposed to coal-dust. Frequently a spot of dust coincided with the position of a tubercle, but more frequently the two formations were distinct from each other.

The masses of intrapulmonary lymphoid tissue are normally situated at the crotch of dividing bronchi and blood-vessels and in or near the pleura, according to Miller (23), and it is in this tissue that tuberculous foci of the lungs usually, if not invariably, originate (24). Under the microscope the lungs of the dusted animals revealed this normal distribution of tubercles, that is, along the bronchi and arteries, especially at dividing points and just under the pleura. The association of dust and tubercle was common in these regions, probably because the latter were in the line of drainage, and both forms of particulate matter, dust and bacilli, were brought there and focalized. But there were numerous areas of tubercle in which no dust could be found in serial sections. In the subpleural

tubercles dust was frequently present and about as often absent. No tubercle was seen in one of the large subpleural collections of dust.

In the study on coal dust (2) it was noted that the anatomical reaction of the lungs to the dust was conspicuous by its absence. The same thing caught Gardner's attention with carborundum dust, and our guinea pigs that had been under exposure to *Crystolon* (silicon carbide) for three years also showed essentially no reaction to the dust either in the lungs or tracheobronchial lymph nodes. No fibrosis could be detected in the lungs and only occasionally could it be demonstrated in the walls of the bronchi and blood-vessels. A few strands of fibrous tissue could occasionally be found in the tracheobronchial lymph nodes. It is true that three years represents a long span in the life of a guinea pig, and from that standpoint more tissue changes might have been expected. But it is to be remembered that the development of industrial pneumonokoniosis in human beings requires years, and with some dusts many years, of exposure (at least a minimum of five years for silicosis). And, although *Crystolon* (98 per cent silicon carbide) does not appear to have irritating qualities for the lungs of guinea pigs under the conditions of the experiment, it does not follow that longer contact with the dust might not produce more pronounced tissue changes. As for the influence exerted by this siliceous dust on tuberculous infection, the most one can say is that there was a suggestion of more tuberculosis in the dusted animals.

SUMMARY AND CONCLUSIONS

1. Guinea pigs were exposed for over three years to the inhalation of heavy atmospheres of a so called "hard" dust, made up mostly of silicon carbide (98 per cent).

2. The effects on the pulmonary tissues were unexpectedly slight in view of the character of the dust and the prolonged contact with it.

3. Guinea pigs thus exposed to silica dust did not appear to be unduly predisposed to pulmonary tuberculosis upon artificial infection.

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TUMOR-LIKE STRUCTURES IN THE LUNGS OF GUINEA PIGS ARTIFICIALLY EXPOSED TO SILICA DUST[1]

HENRY STUART WILLIS AND PAUL BRUTSAERT

In the course of an experiment (1) concerned with the prolonged inhalation of silicon carbide by guinea pigs, several animals presented abnormal tissue, that resembled very closely tumors of the bronchial mucosa, and which forms the subject of the present report.

It appears that tumors in domestic animals were observed by the ancients. In more modern times, Huzard (2) (1801) called attention to their frequency in carnivora. Their occurrence, spontaneously, in the lungs of experimental animals, especially mice, has been reported by Haaland (3), Tyzzer (4), Murray (5), Slye, Holmes and Wells (6), Livingood (7), and a good many others. Murphy and Sturm (8) described similar structures in the lungs of mice following the cutaneous application of coal-tar, and Gaylord (9) thought he produced a malignant tumor of the lung by the injection into a guinea pig of ascitic fluid removed from a case of human peritoneal carcinomatosis.

Aside from Gaylord, the only reference found to tumors of the guinea pig was that of Sternberg (10), who gave a good description of an adenomatoid structure in the lungs of these animals, and attributed it to an abnormal bronchial branching, which, according to him, must be thought of as occurring occasionally in normal animals.

Altogether in our observations there were 7 cases among 80 guinea pigs; and it seems significant that the condition was noticed only among guinea pigs exposed to silicon dust and not in any animals of other experiments or in normal animals. The animals with the tumor-like formations had been exposed to a dust which was 98 per cent silicon carbide. They were subjected to the inhalation of the dust three or four days a week, the average exposures amounting to about 50 hours a month. None was exposed less than 18 and none more than 31 months. Had the incidence not been so high in the "dusted" animals alone, the anomaly

[1] From the Kenneth Dows Tuberculosis Research Fund of the Johns Hopkins University and Hospital, Baltimore, Maryland.

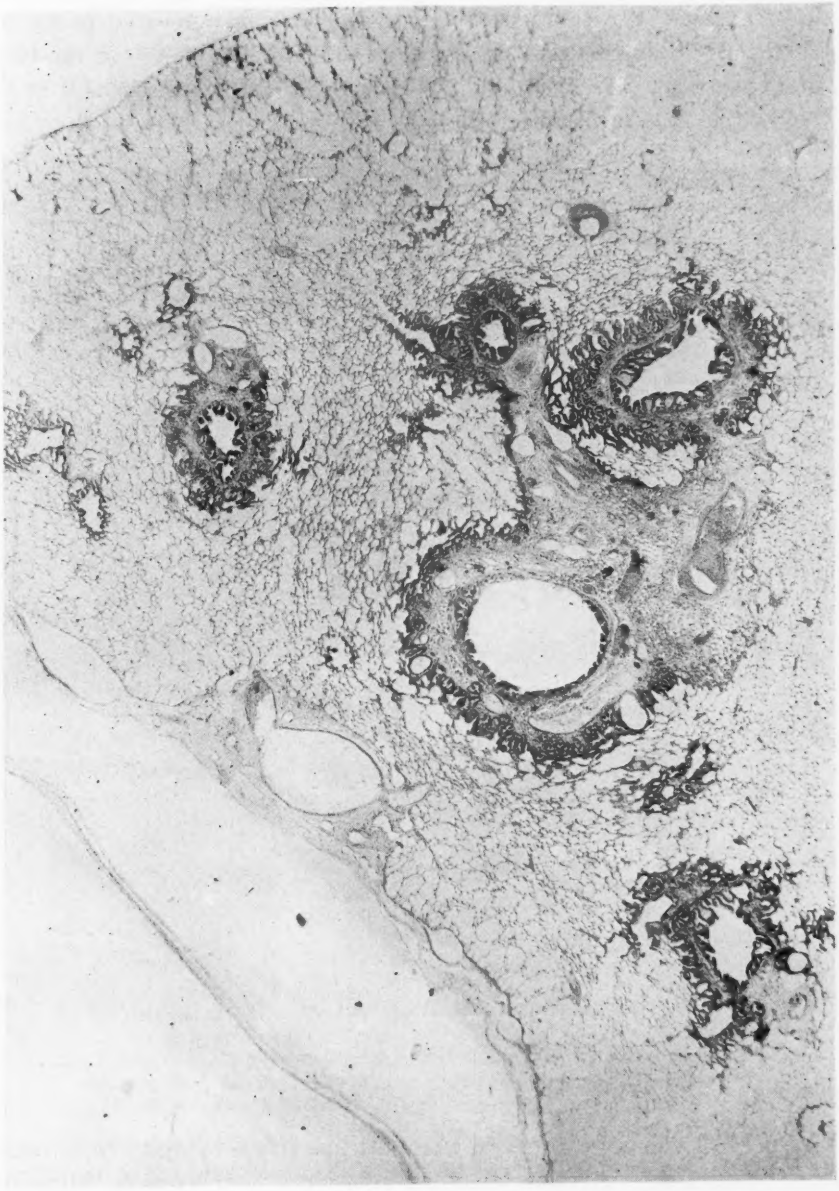

FIG. 1. LOW-POWER PHOTOMICROGRAPH OF SECTION SHOWING MUCOSA-LIKE GROWTH AROUND THE BRONCHI

(?) might have been regarded as having occurred spontaneously and incidentally. The tumor, if we may call it such, appeared in various stages of development in the different animals involved. In the lungs of two of them it consisted of a very considerable overgrowth of the epithelium of alveoli that abut against bronchi, in such a way as to form

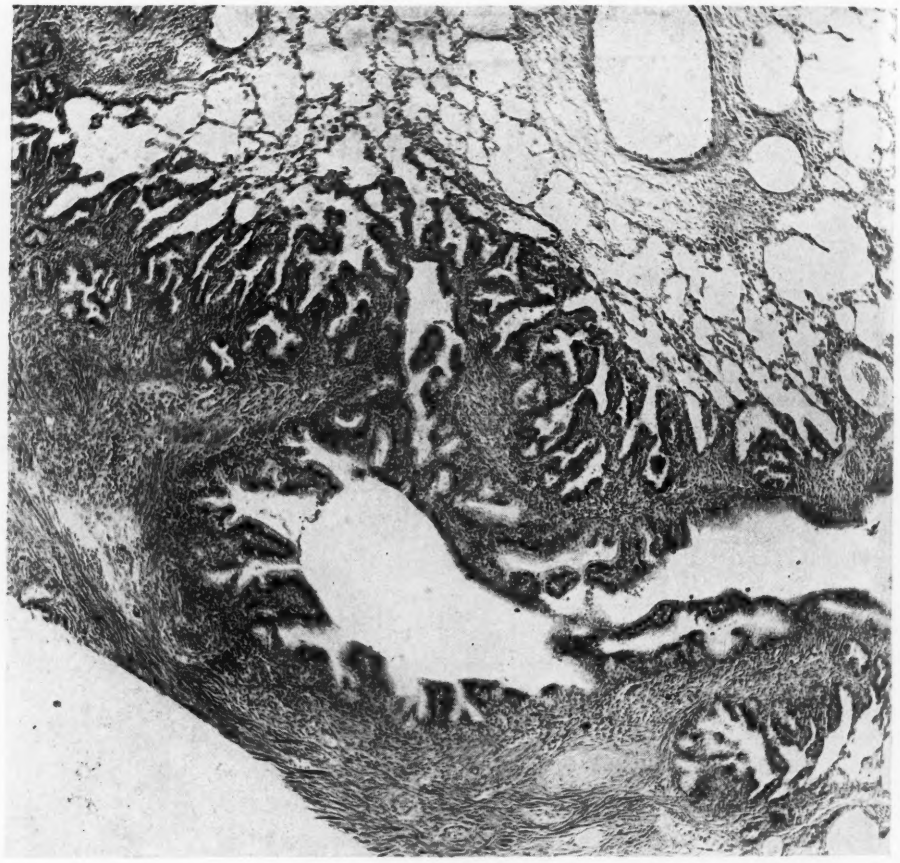

FIG. 2. PHOTOMICROGRAPH OF SECTION SHOWING REDUNDANT MUCOSA AND THICK ADENOMATOUS GROWTH THAT GIVES THE APPEARANCE OF INVASIVENESS

great thick collars or rugae of adenoma-like tissue completely surrounding bronchi and, at times, showing invasive properties, as is illustrated in figures 1 and 2. In some of the sections the condition was as if rugae of the mucosa both surrounded and lined the bronchus. In these fully developed tumors the changes extended throughout all the lobes

of the lung and in uniform degree, giving the impression that all bronchi were enveloped in a sleeve-like sheath of epithelial cells. In one animal the bronchial lining consisted of large folds of redundant mucosa (figure 2), which, however, remained in a single layer and had no mitotic figures. In this same animal there were a few places, such as shown in figure 3,

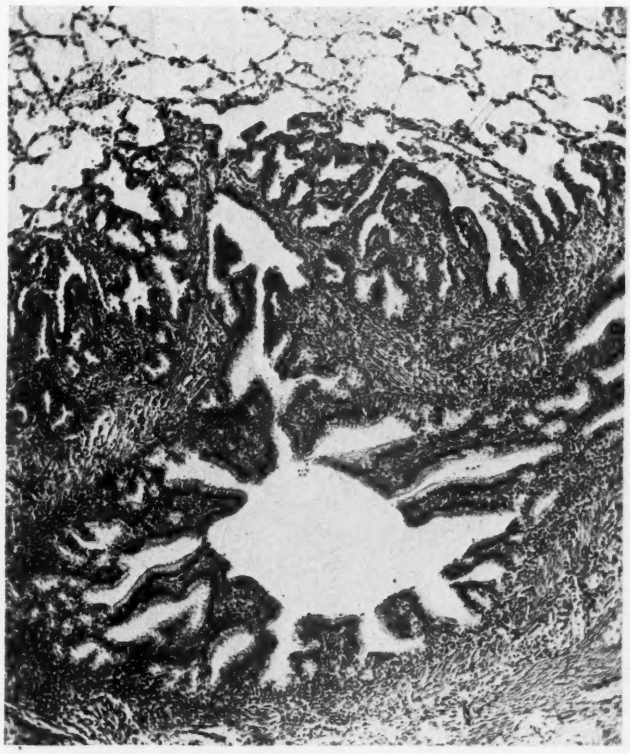

FIG. 3. PHOTOMICROGRAPH OF ANOTHER SECTION IN THE SERIES A SHORT DISTANCE FROM THAT SHOWN IN FIGURE 2

A communication is apparent between the lumen and the air-containing space in the tumor and suggests an abnormal branching

in which there could be demonstrated an actual connection between the cauliflower growth outside the bronchus and the mucosa. There were several places where the new structure lay quite near the *muscularis*, and in which one felt that the next section must surely show a connection with the mucosa, but only these few could be demonstrated even after examination of many serial sections. Occasionally we encountered a

bronchus (figure 4), in which numerous mucosal pouches appeared to have pushed out into or through the muscle and into the adventitia, where, in section, distal portions of them frequently resembled the mucous glands of the lungs of human beings. Normally, however, it may be noted, such glands do not appear to be present in guinea pigs.

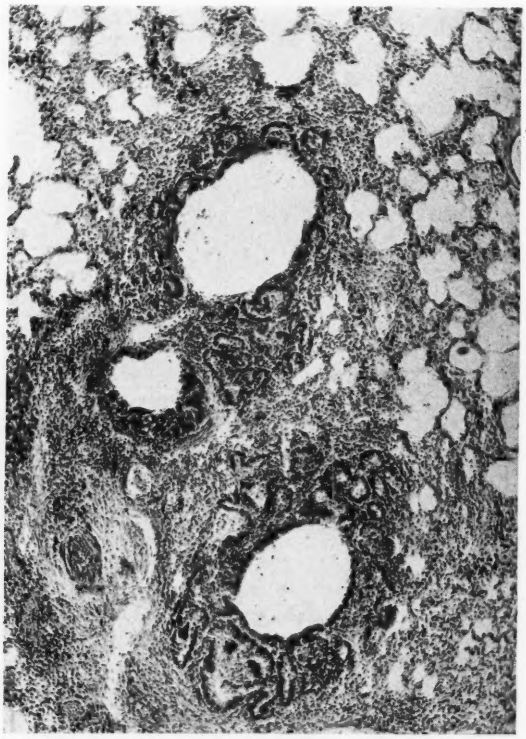

FIG. 4. PHOTOMICROGRAPH SHOWING POUCHING, GLAND-LIKE APPEARANCE OF THE MUCOSA
Further description may be found in the text

In other lungs, with the process apparently in an earlier stage of development, some of the alveoli lying adjacent to bronchi were composed of thickened, cuboidal or even columnar epithelial cells, particularly in the portion immediately touching the bronchial wall. In the same sections a noticeable number of cell-nests were lying in the bronchial adventitia. These bore considerable resemblance to the large epithelial cells lining the alveoli and, in serial sections, were seen to connect fre-

quently with the latter. Yet no connection between these cells and the mucosa could be demonstrated.

Although no unequivocal connection between this tissue and the bronchial mucosa could be determined in this latter group of animals, peculiar breaks or interruptions in the *muscularis mucosa* were frequently

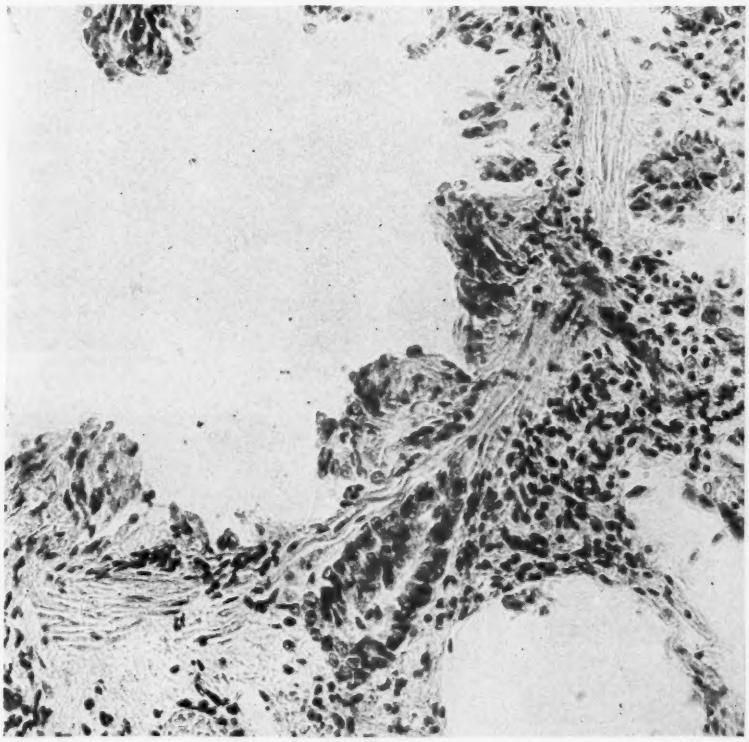

FIG. 5. PHOTOMICROGRAPH SHOWING "STREAK" OF CELLS THROUGH THE *Muscularis Mucosa*
Other large cells are also present

noted, especially where the tumor was in its early stages. In these there frequently could be observed a few large cuboidal cells, which tended to be ranged in straight lines that traversed the muscle. Through some of these breaks capillaries passed, but these large cells could not be interpreted as being capillary endothelium. They frequently joined the thickened alveolar cells; they came near to the mucosa but never were seen in actual contact with it. One of these breaks is illustrated in

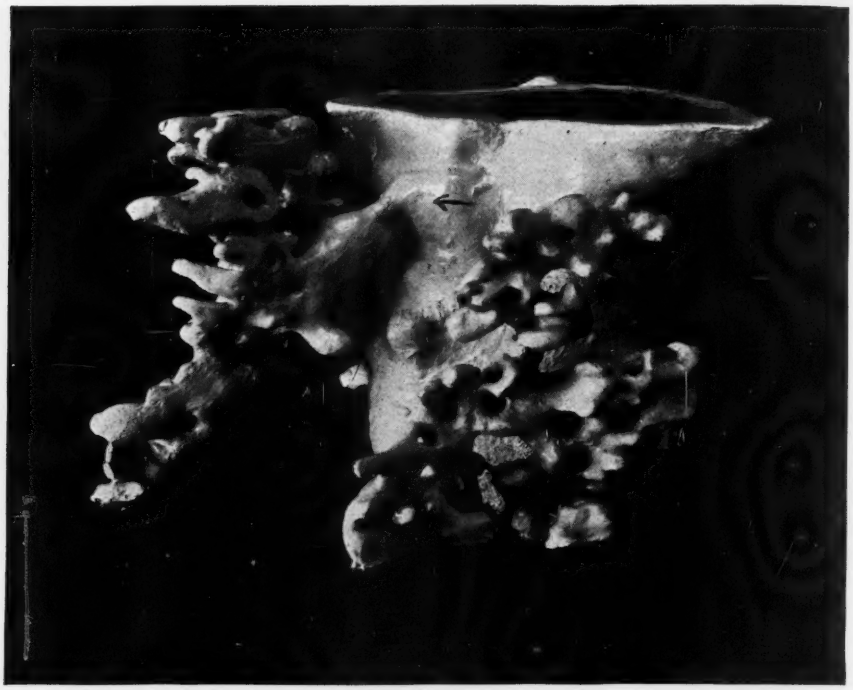

FIG. 6

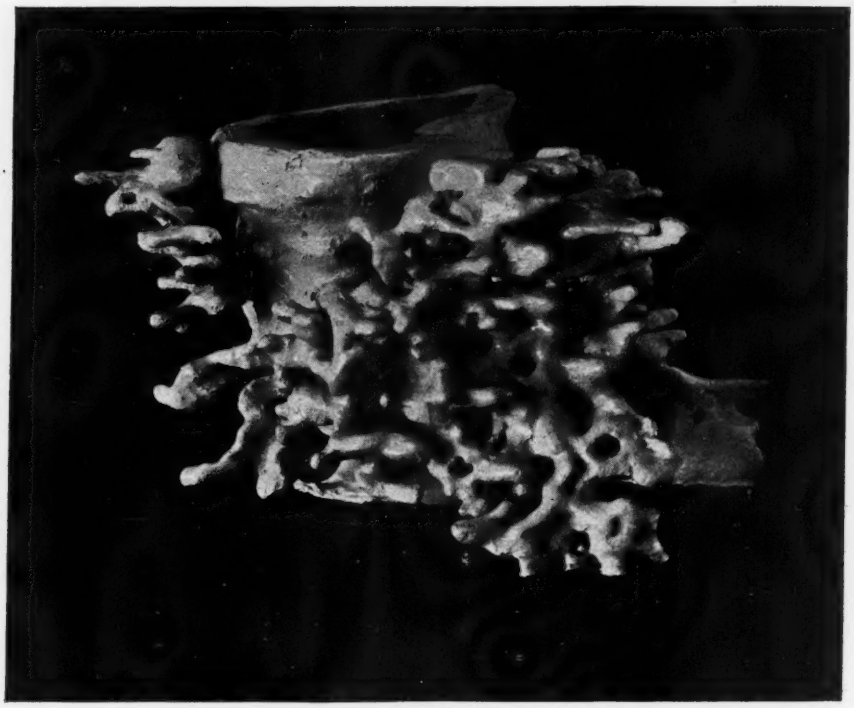

FIG. 7

FIGS. 6 AND 7. TWO VIEWS OF RECONSTRUCTION MODEL

For description see text

figure 5, which also shows some of the large cells just mentioned and a few of the thickened alveolar walls.

In none of the sections from any of the lungs could mitotic figures be found, either in the tumor-like tissue or in the mucosa of the bronchi.

In an effort to learn more of these relationships, a model in wax was made from drawings of serial sections, and photographs of the model

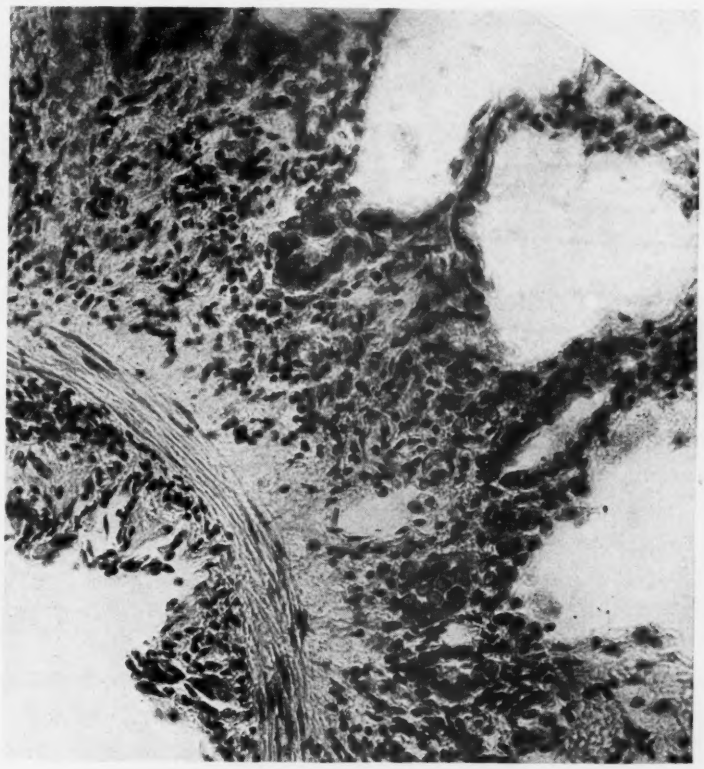

FIG. 8. PHOTOMICROGRAPH OF SECTION ILLUSTRATING THE THICKENED ALVEOLAR WALLS THAT CORRESPOND TO PORTIONS OF THE HONEYCOMBED STRUCTURE TO BE SEEN IN THE MODEL (FIGURES 6 AND 7) × 300

appear in figures 6 and 7. As may be seen from these figures, the bronchus, represented by the thick, solid, central portion of the model, is partially surrounded by groups of finger-like protuberances connected together into a few stems, which appear to join the bronchus and which, when viewed from a plane that places them directly between the observer and the bronchus, present a honeycombed appearance. The small

outer surfaces of the components of this honeycombed structure correspond to the thickened alveolar epithelium and constitute arcs of numerous circles, which, if completed, would correspond to alveoli such as are seen in figure 8.

One of the sections from the level indicated by the arrow is shown in figure 9. The mass of cells lying in or against the *muscularis* in the

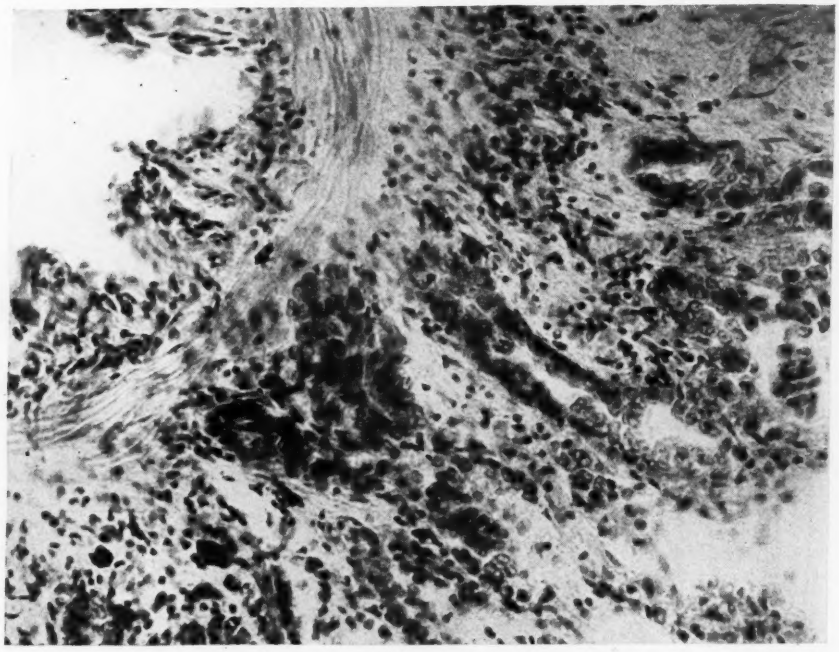

FIG. 9. PHOTOMICROGRAPH OF SECTION CORRESPONDING TO THE LEVEL INDICATED BY THE ARROW IN FIGURE 6

latter illustration is shown as the bulky portion of the link, which, in the model (figure 6), appears to connect tumor and bronchus.

DISCUSSION

The question of interest in the tumor-like process just described is whether it is a real adenocarcinoma, an abnormal bronchial branching, or simply a hyperplastic state of the alveolar epithelium. The apparent invasiveness of the growth, as it appears in figures 2 and 3, certainly gives the impression of a malignant growth. On the other hand, the growth is not massive, or nodular or discrete; it is widely distributed and

more or less uniformly so, following the bronchi in most or all of the lobes; again, all areas in a given lung appear to be in essentially the same state of development, and not as one would expect if metastases had occurred and shown the necessary unevenness in growth that accompanies this.

It is conceivable that, as shown in figure 3, there is an abnormal branching, which, in the presence of a heavy, redundant mucosa, might take on the character shown in the various figures. The cupping of the mucosa (figure 4) and the connection shown in figure 3 would tend to support it; but only these two animals showed such a connection and it may well be that, with a collar of thickened cells already about the bronchus, the small branches simply pass into the former rather than stand in causal relationship with it.

It seems altogether unlikely that the structure is or has anything to do with bronchial mucous glands.

The question arises as to whether, in addition to an overgrowth of the bronchial mucosa, there has been a metaplasia of the alveolar epithelium, due perhaps to the influence of so unyielding a structure as a fibrotic bronchial wall nearby; for, as has been stated, the process described has been particularly prominent in alveoli which are in proximity to and abut against bronchi (though not connected with them). Gardner[2] has noted more or less similar reactions on the part of the epithelium about healing, fibrotic tubercles after inhalation-infection with a strain of tubercle bacillus of low virulence. In some of his experiments the epithelium of an alveolus lying next to the tubercle, which was becoming converted into a fibrous wall, frequently had become cuboidal in that portion that was in actual contact with the mass, the mucosa remaining normal elsewhere. But, in the 80 animals of our dust experiment, of which these seven were a part, there was usually but slight evidence of fibrosis of the bronchial walls.

No satisfactory explanation of the phenomenon can be offered; but it would appear that the epithelium of the bronchial mucosa (and possibly that of alveoli that lie close to bronchi) have undergone a hyperplasia as the result of irritation set up by the inhaled dust.

[2] Personal communication.

SUMMARY

1. In 7 of 80 guinea pigs, subjected to the prolonged inhalation of atmospheres of silicon-carbide dust, there were found tumor-like structures of the bronchial mucosa.

2. The lungs exhibited few evidences of a fibrous reaction, such as would be expected from the long-continued irritation of the dust.

3. Similar tumor-like structures have never been observed by the authors in an extensive experience with experimental studies of the lungs of other guinea pigs.

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THE DIAGNOSIS OF TUBERCULOSIS BY MEANS OF THE HAMSTER[1]

JOHN H. KORNS AND GEORGE Y. C. LU

Elsewhere (1) we have suggested that the hamster might be used to advantage in China for the diagnosis of certain forms of tuberculosis; and it is possible that laboratory workers outside of China might be interested in introducing the hamster for this purpose. With this in mind further experimental data are here recorded.

The striped hamster (*Cricetulus griseus*) is a small field rodent, weighing about 30 gm., which normally inhabits ground burrows. In Peking it is easily purchased in the market, being supplied by farmers; so we have not attempted breeding it in the laboratory, although it is probable that this could be done, as young litters have been found in refuse into which the hamsters have escaped (2). The initial cost and the cost of upkeep of the hamster in Peking is about one-tenth that of the guinea pig. The hamster has a low mortality under laboratory conditions, and with care can be transported to distant points. In over 12,000 autopsies of hamsters Young and Hertig have not observed spontaneous tuberculosis (2).

The hamster has been found very susceptible to *Leishmania donovani* infection, and has proved a most useful laboratory animal for experimental work with these microörganisms. In the hamster and in the human body these protozoa are phagocytized by the same type of cell which seems to figure largely in phagocytizing tubercle bacilli and in starting tubercle formation. This observation led us to investigate the susceptibility of the hamster to tuberculous infection, and we have found (3) it to be much more easily infected than the white mouse, using both bovine and human strains; and, while the guinea pig shows lesions that are more striking grossly, the hamster's tissues show more tubercle bacilli. This is in line with observations of those who have worked with other species of mice (4).

In the work here reported the material inoculated consisted of sputum,

[1] From the Department of Medicine, Peking Union Medical College, Peking, China.

serous exudate, tonsils and pus from patients on the clinical services in this hospital. The inoculations were in all instances made subcutaneously into the groin. The hamsters were then caged separately, to prevent cannibalism and cross infection, and after five to eight weeks were examined postmortem.

Sputum: Eighteen specimens of sputum were inoculated. The routine was to digest the sputum in 3 per cent sodium hydrate at 37°C. for a half-hour, neutralize with hydrochloric acid, centrifugate and inject 1 cc. of the sediment. Four specimens, negative for tubercle bacilli in from one to three ordinary smear examinations and one to ten examinations after concentration, all produced tuberculosis in the hamster. Three specimens, negative in smears and negative in hamsters, came from patients who later recovered and were shown to have had bronchitis and bronchopneumonia. Eleven specimens which were positive, either by direct smear or after concentration, all caused tuberculosis in the hamster. None that was positive by microscopic examination failed to produce tuberculosis in the hamster.

Serous Exudate: Eighteen specimens of pleural and one of ascitic fluid were inoculated. The routine was to collect from 50 to 100 cc. of exudate, in a small amount of sodium-citrate solution, centrifugate rapidly for 30 minutes, and then inoculate 1 cc. of the sediment. None of the 18 specimens showed tubercle bacilli on microscopic examination. Seven of the specimens of pleural and one of ascitic fluid caused tuberculosis and eleven failed to produce it in the hamster. As controls for the 11 negative hamsters, 11 guinea pigs, inoculated with from four to ten times the amount of material used for the hamsters, were all negative.

Tonsils: Ten tonsils were halved, one-half of each being sectioned for microscopic study, and the other half triturated and suspended in salt solution for inoculation. Of the 10 hamsters injected two were positive, and these checked with two positive guinea pigs, although the histological report on single sections of the tonsils stated that there was no tuberculosis. Eight were negative, six of which had negative guinea-pig controls. Two of these six, though negative, had been inoculated with tonsils which showed histologically caseous tubercles, in which no acid-fast bacilli were seen.

Pus: Thirteen hamsters were inoculated with pus from suppurating lymph nodes or cold abscesses. Five of them were positive, although no acid-fast bacilli could be seen in smears of the pus prior to inoculation.

Four were negative; in these instances the pus came from three cases that were clinically tuberculous and one that was not. The pus of one of the three caused sloughing of the whole hind leg of the hamster, thus rendering it unfit for further use. Four hamsters, which had been inoculated with pus that was positive on microcscopic examination, were positive; and in no instance in which tubercle bacilli could be demonstrated in smears did the pus fail to infect the hamsters.

As to the type of lesions observed it should be said that they are smaller than in guinea pigs and therefore less striking in the gross. The lungs usually show the most characteristic lesions which appear as pellucid areas of pin-point to pin-head size on the surface. The tracheobronchial lymph nodes and spleen are perceptibly, often markedly, enlarged. On microscopic examination the lesion is seen to be almost wholly proliferative in type. Less caseation is seen than in the guinea pig, and there is but slight tendency to giant-cell formation. On the other hand, tubercle bacilli are usually found in abundance in the lesions. This offers a real advantage over the guinea pig, in whose tissues the bacilli are sometimes difficult to demonstrate. In the hamster it is often possible as early as two or three weeks after inoculation to remove an inguinal lymph node and, by crushing and staining, demonstrate acid-fast bacilli.

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SURGICAL REST IN PULMONARY TUBERCULOSIS[1]

The Most Recent Advance in Phthisiotherapy

CASPER F. HEGNER[2]

Rest is the foundation of successful phthisiotherapy.

The therapeutic result is proportionate to the degree of rest attained. To be of utmost therapeutic value rest must be physical, physiological and psychic.

Brehmer and particularly Dettweiler (1) inaugurated the first rational step in the treatment of tuberculosis when they advocated systemic physical rest to conserve vital energy.

Carson (2), in 1821, noted the beneficent effect of penumothorax on a diseased lung. Cognizant of its value in securing local relaxation and rest, he recommended the induction of graded pneumothorax in the treatment of pulmonary tuberculosis.

Forlanini (3), in 1884, by his teaching based on clinical experience, firmly established induced pneumothorax as a therapeutic procedure.

Induced pneumothorax, securing physiological or local rest, marked the second forward step in the treatment of pulmonary tuberculosis.

Unfortunately, it is not always possible to induce or to maintain a satisfactory degree of pneumothorax. In some cases it may become a menace rather than an aid.

Brauer (4) noted the striking improvement consequent to the successful induction of pneumothorax in cases of largely unilateral pulmonary disease. Appreciating the principle of collapse therapy, he saw the possibility of securing relaxation and rest of the lung by surgical compression in similar cases in which it was impossible to induce pneumothorax.

Surgical relaxation and compression constitute the third and most recent advance in phthisiotherapy.

Surgery is not a substitute for any of the older forms of treatment. It is a supplement to all the accepted procedures, when these have failed,

[1] Read at the annual meeting of the Nebraska State Medical Association, Lincoln, Nebraska, May 10–12, 1927.

[2] Denver, Colorado.

or, judged from experience, will probably prove ineffective in reëstablishing a "resistance balance" against the disease (Hegner (5)).

To be of value in pulmonary tuberculosis, surgery must be invoked before the patient's reserve is depleted.

We have learned the necessity of early operation in cancer, of the advantage of operating during the rising tide of reserve in thyrotoxic states, and of the diminished hazard in multiple-stage operations in properly prepared prostatics. These facts must be applied in the surgery of pulmonary tuberculosis.

The interests of the patient can be best served by the coöperation of the phthisiologist, who earlier recognizes the limitations of his therapy, and the surgeon, who appreciates the substandard character of these surgical risks.

Surgical procedures are

1: Avulsion of the phrenic nerve: Phrenic avulsion.
2: Direct compression of the most diseased areas
  a: Extrapleural pneumolysis.
  b: Intrapleural pneumolysis.
3: Direct relaxation of the most diseased areas or cavities: Limited thoracoplasty.
4: Indirect or massive compression (extensive deossification of one-half the thorax): Extrapleural paravertebral thoracoplasty.

Phrenic avulsion (exairesis, Felix (6)) is the extraction of the intrathoracic portion of the phrenic nerve through an incision at the base of the neck. It is a well-recognized and thoroughly tested operation. It may lead to striking improvement; rarely does it effect a cure. Its good effects are often but temporary. It is a valuable adjunct to induced pneumothorax and an efficient supplement to surgical collapse.

The purpose of phrenic nerve avulsion is to secure localized rest by paralyzing the corresponding half of the diaphragm.

Paralysis of one-half of the diaphragm eliminates its piston-like action with each respiratory cycle, lessens the inspiratory phase of the base of the lung, and obviates the dangers of stasis and aspiration of secretions and pneumonia.

Atrophy, and consequent upward doming of the diaphragm, when not held by adhesions in the costophrenic angle, compromises the capacity of the corresponding half of the thorax $\frac{1}{6}$ (400 cc.) to $\frac{1}{3}$ (800 cc.). This volumetric diminution is a decided advantage. Elimination of the

tug and ascent of the diaphragm relaxes pleuritic adhesions at the base, as well as fibrous bands not only at the base but also those extending upward toward the apex of the lung. The gaseous interchange in the corresponding lung is diminished, and its circulation of blood and lymph retarded. By this stasis the toxins within and about the lesions are kept more localized. The lung is in a state of partial rest.

The paralyzed, atrophied diaphragm offers little resistance to intra-abdominal pressure. The upward unimpeded force of the abdominal press makes coughing easier and more productive; hence, less frequent. The amount of sputum diminishes and changes in character with the improvement of the lesions.

Because of the stasis of blood and lymph within the lung, and the inhibition of the pump-like action of the paralyzed diaphragm, the absorption of gases, air or fluids from within the pleural space is materially restricted. This is of importance in artificial pneumothorax, for the necessity for refills is less frequent.

Intrapleural tension being reduced and adhesions relaxed, the effect of induced pneumothorax is intensified by favoring the selective compressing action of the introduced air. Greater compression with lower air-pressures can be obtained, and the danger of complications is minimized.

The diminished gaseous interchange within the lung on the paralyzed side throws a greater amount of work on the contralateral lung. Accordingly, phrenic-nerve avulsion becomes a valuable test of the contralateral lung's capacity to assume the burden of respiration without reactivating quiescent or suspicious lesions. It is then serviceable as an index regarding the advisability of performing more formidable operations for surgical collapse when the status of the opposite lung is in doubt.

Indications for phrenic-nerve operations:

As an adjunct to pneumothorax.

A test of the status of lesions within, and the respiratory capacity of, the contralateral lung, preliminary to the more formidable surgical collapse, particularly if one wishes to do only a resection of the upper ribs, or perform an upper-stage thoracoplasty first.

Lower-lobe lesions, bronchiectatic or tuberculous. The advantages are not confined to lower-lobe lesions, but are more pronounced in their case.

To control repeated haemoptysis.

Extensive unilateral disease with slightly active or quiescent lesions in the opposite lung.

As a palliative measure to control toxaemia, and to assuage cough in desperate cases with preponderating lesions in the corresponding lung.

Operations on the phrenic nerve are comparatively safe. For permanent paralysis at least four to four and one-half inches of the nerve must be withdrawn. This will interrupt the conductivity of accessory phrenic nerves, which are present in 20 to 25 per cent of individuals.

The benefits, which include resting the lung, relaxing adhesions, thus favoring the collapse and contraction of cavities, controlling and making more effective the cough, diminishing the amount of sputum, and depressing toxaemia, are pronounced.

Extrapleural pneumolysis is localized direct compression of a diseased area or cavity. This is accomplished by bluntly separating (preferably digitally) the endothoracic fascia and parietal pleura from the ribs through a small opening (the smaller the better) in the thoracic wall. The resulting extrapleural space may be filled with fat (Tuffier (7)), muscle (Archibald (8)), gauze (Lange (9)), or plastic wax masses (Baer (10)).

Extrapleural pneumolysis, with or without filling the extrapleural space, is uncertain in its ultimate result. The operation is incomplete, and has all the disadvantages of partial procedures and the added dangers of infection, ulceration, rupture of the cavity, and haemorrhage.

Indications for extrapleural pneumolysis:

Apical or localized firm-walled cavities in a well-fibrosed lung with scanty positive sputum.
Unilateral or bilateral apical cavities in cases too ill for more formidable operations.
Residual cavities after thoracoplasty which corrective operations have failed to collapse.

Closed, or intrapleural pneumolysis, according to the method of Jacobaeus (11) is the cutting by the electrocautery of thin, firm, isolated adhesions within the pleural space. It is theoretically a splendid procedure. Intrapleural pneumolysis is indicated in exceptional cases with isolated, slender, firm pleuritic adhesions which interfere with massive collapse of the lung by pneumothorax. The risks, such as haemorrhage, effusion, empyema, bronchial or pulmonary fistula, scarcely warrant the attempt. It is contraindicated whenever cavities of any size are present in the lung, and when pleuritic adhesions of considerable size and extent are present.

The direct surgical attack of lesions in the lung was proposed by Bary. DeCerenville (12), in 1885, relaxed cavities by resecting parts of the overlying ribs. He was only partially successful. His resections were not sufficiently extensive.

The resections of lateral segments of ribs, according to Estlander (13) and Schede (14), were devised and performed to collapse empyema cavities. Even though the resections are extensive, the effect is a comparatively limited collapse. The inherent outward elasticity of the rib is augmented by the contraction of the auxiliary muscles of respiration. This outward spring of the resected rib-ends is unopposed when the rib is resected in the area of greatest convexity. The remaining anterior and posterior stumps serve as points of attachment for the auxiliary respiratory muscles, and form rigid, deforming buttresses which interfere rather than favor collapse of the thorax or compression of the lung.

Boiffin and Gourdet (15), in 1885, improved upon any previous obliterative empyema operation by making resection of the ribs posteriorly as close to the spinal column as possible. Only the anterior segment of rib was left. This was in the most pliable part of the rib, which yields readily to external pressure and to the inward traction of adhesions. The posterior stump being completely removed, the costovertebral groove is more effectively compromised.

The Boiffin-Gourdet thoracoplasty was devised primarily for the obliteration of empyema cavities, without thought of pulmonary compression. The degree of collapse of the chest is greater and more uniform, and the compression of the lung most efficient. It is practically the same operation named by Spengler (16) *extrapleural paravertebral thoracoplasty*, the standard operation for surgical compression of the lung.

Brauer (4), working with Friedrich, applied the principles of obliterating-empyema operations to secure compression of the lung. Friedrich performed the first operation for compression of the lung in 1907. He removed the ribs with their periosteum and muscles. In 1911, this operation was modified to a subperiosteal resection of long segments of the first to tenth ribs. Brauer does not always remove the first rib. He removes long segments of the other upper ribs and short segments of the lower ribs. He retains the eleventh rib with a view of stabilizing the diaphragm and minimizing mediastinal flutter.

Sauerbruch (17), in 1909, was the first to recognize the importance of resecting the first rib, and advised attacking it from behind. He also emphasized the importance of resecting all the ribs as close to the spinal

column as possible, in order to obliterate the costovertebral groove. Resection of one inch posteriorly has greater relaxing effect than three inches anterior to the angle of the rib.

Appreciating the dangers of respiratory and cardiac embarrassment consequent to resection in a single stage of even short segments of all the ribs, Sauerbruch recommends two stages, and in extreme cases multiple-stage operations. The reduction in operative hazard increases the applicability of thoracoplasty.

The single-stage total thoracoplasty is the ideal operation. The collapse is immediate, uniform and extensive. But the operative risk and immediate postoperative dangers are so great that it is seldom justified. Two or more stages at short intervals (two or three weeks) are much safer, especially when, as must often be the case, the resistance of the patient is low.

The lower ribs should be removed as a first stage, even though these be over the lesser involved area, in order to obviate the danger, during the early postoperative days, of aspiration infection and pneumonia in the lower lobe or in the contralateral lung.

The frequency of aspiration infection is denied by most operators who resect the upper ribs first. They maintain that the cough reflex is less inhibited and the retention of secretions is less after an upper first stage. The cough reflex is inhibited to an equal (if not a greater) degree in an upper first-stage as in a lower first-stage operation. The physics of compression make aspiration infection and pneumonia following an upper first stage strong possiblities. This fact, substantiated by extensive experience, prompts Sauerbruch and many others to perform, as a routine, the lower stage first.

An upper first stage may be safely performed when the lower lobe is controlled by a partial artificial pneumothorax until postoperative compression and healing in the upper more diseased area are advanced or complete, after which the lower lobe may be permitted to reëxpand slowly. It is also safe when the base of the lung is controlled by a successful phrenectomy.

Since the intrapleural tension in multiple-stage operations is not uniformly altered, care must be exercised in planning the stages, lest unequal tension in the lung and pleura rupture or tear a cavity or cause haemorrhage. When the area of a cavity is encroached upon, the ribs overlying the cavity and its margins must be removed in one stage, in order to avoid unequal intrathoracic stress.

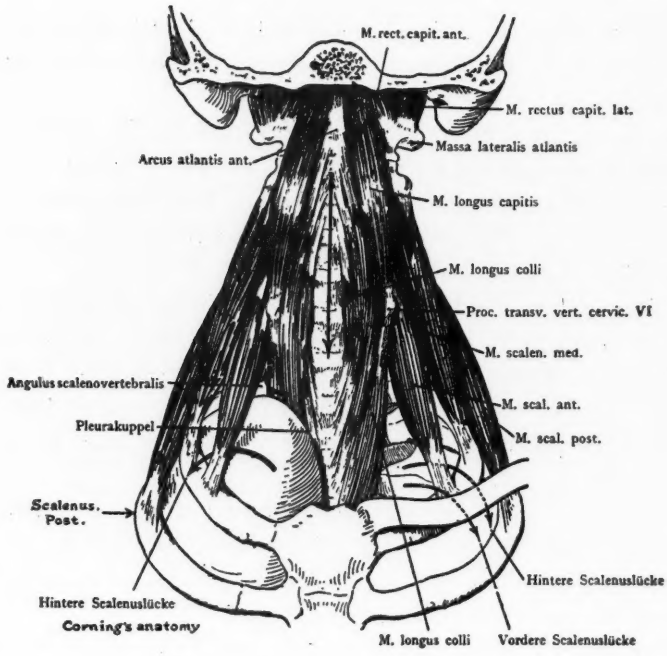
M. rect. capit. ant.
M. rectus capit. lat.
Massa lateralis atlantis
Arcus atlantis ant.
M. longus capitis
M. longus colli
Proc. transv. vert. cervic. VI
M. scalen. med.
Angulus scalenovertebralis
M. scal. ant.
Pleurakuppel
M. scal. post.
Scalenus Post.
Hintere Scalenuslücke
Hintere Scalenuslücke
Corning's anatomy
M. longus colli
Vordere Scalenuslücke

FIG. 1

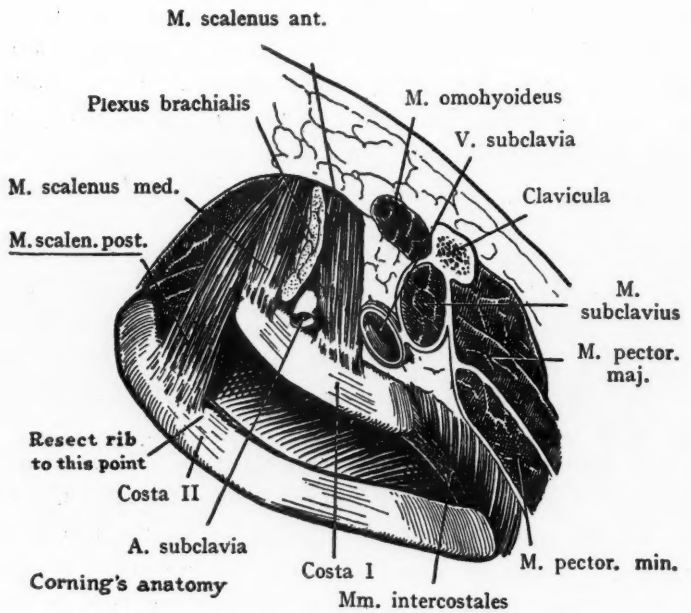
M. scalenus ant.
Plexus brachialis
M. omohyoideus
V. subclavia
M. scalenus med.
Clavicula
M. scalen. post.
M. subclavius
M. pector. maj.
Resect rib to this point
Costa II
A. subclavia
Costa 1
M. pector. min.
Corning's anatomy
Mm. intercostales

FIG. 2

The number of ribs and the lengths of segments to be removed must be governed by the condition of the pleura, the size and extent of the empyema cavity, the presence, size, rigidity and location of intrapulmonary cavities, and the flexibility or rigidity of the thoracic walls.

The thoracic cage is subtended by the first rib and by the attachment of the scalenus posticus muscle to the second rib (figure 1). In order to secure a massive collapse it is always necessary to resect one to one and one-half inches of the first rib and a sufficient length of the second rib to go well forward of the insertion of the scalenus posticus muscle (figure 2). Impinging of posterior ends of the resected first and second ribs on the next lower vertebra will be avoided. Downward, backward and mesial sinking of the other ribs will ensue, assuring an adequate collapse in the upper part of the thorax, where the greatest degree of collapse is usually desired.

The purpose of surgical compression is identical with compression by pneumothorax.

Indications for surgical collapse:

When, on account of adhesions, artificial pneumothorax cannot be primarily induced or is unsatisfactory, or cannot be maintained.

When, after the cessation of pneumothorax, the lung fails to reëxpand or cannot reëxpand to fill the thorax.

When lesions in the reëxpanding lung become active, and the pneumothorax cannot be reinduced.

When there are cases with large cavities. Cavities with rigid walls, with or without pleuritic adhesions, have a doubtful ultimate prognosis under incomplete pneumothorax and should, therefore, be considered surgical much earlier than is now customary.

When recurrent haemoptyses are not relieved by artificial pneumothorax or phrenectomy.

In cirrhotic types with or without cavitation. As long as progress is being made, defer operation. When, for mechanical reasons further progress is impossible, operate. Surgical collapse is then the only measure that can further the process of healing.

In marked fibrosis with mechanical cardiac embarrassment. Thoracoplasty may then serve as a modified cardiolysis.

In desperate cases, one lung so involved in advanced disease that it can never function adds an insurmountable burden. Compression controls the worse lung and releases antibodies, which, concentrating their attack on the lesser lesions, gives the only chance for benefit.

In empyema that cannot be controlled by conservative measures, such as

aspiration, irrigation or closed drainage. Prolonged closed drainage is permissible, but should not be followed by open drainage, except in localized encysted empyemata and after thoracoplasty.
In extensive pyogenic, tuberculous or mixed empyema, with or without pulmonary, bronchial or pleurocutaneous fistula.
In bronchiectasis in the lower lobes that has not been greatly improved by phrenectomy, prior to cautery-lobectomy or drainage.

Continental surgeons prefer local anaesthesia. American surgeons use general anaesthesia, most of them gas-oxygen or ethylene, but a few use ether. With few exceptions, all my cases were performed under nerve-block and local infiltration (novocaine 0.5 per cent), reinforced with morphine (gr. $\frac{1}{4}$) given forty-five minutes before operation. This may be supplemented by gas-oxygen or ethylene during the operation. I am convinced that, under local anaesthesia, the condition of the patient can be better gauged, the cough reflex is not inhibited, the aspiration of secretions is avoided, the oozing of blood in the wound during the operation is less, and the immediate postoperative phase is much better.

The most satisfactory plan of surgical attack is a paravertebral extrapleural resection of four to five inches of the lower five or six ribs, beginning with the eleventh, and resecting as close to the spine as possible. To accomplish this it will be necessary to "rongeur" the posterior rib stumps at the spine. Two or three weeks later, through an upper paravertebral incision, segments in diminishing lengths are resected from the remaining upper ribs. The second rib should be resected anterior to the insertion of the scalenus posticus muscle, which can readily be seen on elevating the scapula from the chest. One to one and one-half inches of the first rib should be removed. This will prevent the posterior ends of the first and second ribs from impinging on the spinal column, which, should it occur, will greatly interfere with adequate collapse. The posterior ends of the resected ribs should be on a fairly even line. I find it convenient to strip or prepare all the ribs to be removed at a given operation before any are resected. The raw ends of the ribs may be coated with bone-wax if postoperative necrosis is considered likely. A large soft-rubber drain of the Penrose type is inserted at the top of the "deribbed" area. The wound is sutured in layers, and a large dressing, under just sufficient pressure to support the "deribbed" area and to hold the raw surfaces in apposition, is applied. Too tight or too loose a pressure is not only uncomfortable but dangerous. It is of paramount

importance that cough and expectoration be encouraged during the first postoperative days. The drain is removed after forty-eight hours, and compression as firm as can be tolerated is begun, and continued for five or six weeks, until the ribs regenerate and, by their altered alignment, support the chest-wall and maintain compression. I find large rubber sponges, placed under firmly drawn adhesive strips (three inches wide), the most resilient and comfortable for compression.

Paravertebral thoracoplasty relaxes and compresses the lung, expresses secretions, exudates and toxins, and prevents reaccumulation. Compression of the lung is at first passive; later, due to the inherent tendency of fibrous tissue within the lung and pleura to contract, it becomes active. Fibrosis is stimulated in the lung and pleura. Respiratory excursions of the thoracic wall are limited. Elastic tension of the intact ribs is abolished by the break in their continuity, and by the change in their shape and alignment. Gaseous interchange in the lung is greatly reduced. There is a marked stasis of blood and lymph. Toxins, after an initial increase, are diminished and kept localized. The lung is at rest. The volumetric capacity of the collapsed side is diminished $\frac{1}{4}$ (600 cc.) to $\frac{3}{8}$ (900 cc.).

Deformity is due to a downward, backward and mesial sinking, a shortening of the anteroposterior and lateral diameters and a diminution in the circumference of the hemithorax. There is a slight rotation and scoliosis of the spine. The opposite side, due to compensatory emphysema, becomes larger. The deformity is well concealed by the shoulder girdle, the clavicle in front, the scapula behind, and a drooping of the shoulder. Deformity is more marked in younger subjects, with more elastic thoraces, and in the thin-muscled. Early postural exercises control curvature of the spine to a great degree. Deformity is not as great as one might expect after so extensive an operation, and is well concealed by the clothing.

Sequence of surgical procedures:

Artificial pneumothorax, supplemented by phenic avulsion. Lower first-stage, upper second-stage paravertebral extrapleural thoracoplasty. Six months to a year later, a corrective paravertebral followed by a parasternal resection (18); pneumolysis with filling; lastly drainage.

Effect on capacity of the thorax (19):

Massive pneumothorax gives massive compression.
Phrenic avulsion decreases capacity of thorax $\frac{1}{6}$ (400 cc.) to $\frac{1}{3}$ (800 cc.).

Complete paravertebral resection decreases capacity of thorax $\frac{1}{4}$ (600 cc.) to $\frac{3}{8}$ (900 cc.).
Phrenic avulsion plus complete paravertebral resection decreases capacity of thorax $\frac{5}{8}$ (1500 cc.).
Phrenic avulsion plus complete paravertebral resection plus parasternal resection decreases capacity of thorax $\frac{3}{4}$ (1800 cc.).

Results are proportionate to the resistance of the individual to the disease, as expressed in degree of pulmonary fibrosis, and to the degree and maintenance of collapse.

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THE SURGICAL TREATMENT OF NONTUBERCULOUS CONDITIONS IN TUBERCULOSIS PATIENTS[1]

STANLEY R. MAXEINER[2]

The reader of present-day medical literature will be impressed with the small number of articles written about nontuberculous lesions in tuberculous patients, if compared with the large number devoted to such popular subjects as tuberculosis of the bowel, thoracoplasty, etc.

In order that nontuberculous diseases may be properly studied and treated in this day of extreme specialization it is important for a sanatorium caring for tuberculous patients to have men trained in roentgenology, general medicine and surgery, either as members of its staff or as consultants. These members must coöperate fully with those of the staff who specialize in tuberculosis.

One must constantly bear in mind that patients with tuberculosis are subject to the same general diseases that other people may have, and that two or more diseases may exist in the same patient at the same time. The writer has seen acute appendicitis go on to perforation undiagnosed in the presence of a bad fracture, pregnancy and tuberculosis when the appendicitis would have been recognized promptly if it had existed alone. It is important for clinicians treating such cases to study each one carefully, and not content himself by merely stating that the inability to handle food, the vomiting, or the abdominal pain is due to the toxaemia of tuberculosis. We believe that every tuberculosis patient with abdominal symptoms is entitled to careful study and a differential diagnosis when possible.

Except in emergencies such cases are referred to our gastroenterologist, who obtains a painstaking history of the abdominal complaint. Laboratory examinations of stomach contents, stool, urine, blood, etc., are completed, and in turn the patient is referred to our radiologist. Patients presenting surgical lesions are then referred to the surgeon, who reviews all findings and makes his recommendations. A consultation

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of gastroenterologist, surgeon and specialist in tuberculosis designates what course is to be pursued, but the chest specialist should determine finally whether the patient's pulmonary disease contraindicates surgery. In numerous instances our radiologist has been able to demonstrate gastric or duodenal ulcer, deformity due to gall-bladder disease and extensive visceroparietal adhesions in previously operated cases through the aid of pneumoperitoneum. In conjunction with the usual clinical and laboratory examinations we have used cholecystography with satisfaction in our gall-bladder cases. The X-ray, through the medium of the opaque meal and barium clysma, helps to differentiate appendicitis from tuberculosis of the caecum and ileum We have found the leucocyte count very high in some cases of tuberculosis of the bowel that resembled appendicitis and, as a result, consider it of far less importance than in nontuberculous subjects.

It is obvious that emergency operations must be undertaken under adverse circumstances, while operations of choice, such as herniotomy, should be reserved for those in good condition. However, it has been a revelation to see how well tuberculosis patients endure surgery under local anaesthesia. Even advanced cases have undergone extensive operations without any evidence of exacerbation of their pulmonary disease. Indeed, in some instances there has been actual improvement, due to more enforced rest and the fact that any patient can combat one lesion better than two.

In order to use local anaesthesia successfully, the surgeon must first acquaint himself with the methods of injection, and, second, with that more highly developed surgical technique which the method demands. In fact we feel that the gentle handling of tissues, with its reduction of trauma, shares equally with local anaesthesia in the elimination of shock and postoperative distress. The surgeon must likewise use the method daily, and not occasionally, if he wishes to be proficient. As is so frequently claimed, we have not been handicapped by the use of local anaesthesia in the performance of our operations, although we have repeatedly explored both the upper and lower abdomen, and have removed the gall-bladder and appendix at the same operation.

The writer during the past two years has performed 64 major operations for nontuberculous lesions on patients with tuberculosis as follows: Appendicectomy; cholecystectomy; drainage of the common duct for obstruction; gastric resection; gastroenterostomy; herniotomy, inguinal, femoral and postoperative; resection of the lip and bloc dissection of the

neck for malignant tumor; thyroidectomy for toxic adenoma; exophthalmic goitre, etc.

In addition to these he has performed more than 125 other minor operations for nontuberculous, and major and minor operations for tuberculous conditions.

Sixty-two of these 64 major operations were performed satisfactorily under local anaesthesia alone. Two cases only required the addition of gas for a short time. All of the other 125 operations were done under local anaesthesia alone.

A brief report of 3 cases will best serve to illustrate what I have attempted to bring out in this paper.

Cases

Case 1: Mr. E., age 32 years, male, single. Family history negative. *Present Complaints:* (1) Loss of appetite and weight, cough and expectoration. *Diagnosis:* Pulmonary tuberculosis, moderately advanced, arrested. (2) Attacks of stomach trouble with fulness, belching and distress after meals, for two and one-half years, which were not relieved after removal of his appendix two years ago. *Diagnosis* of penetrating gastric ulcer was confirmed by X-ray. Under local and anterior splanchnic anaesthesia a sleeve resection was performed for a large penetrating ulcer on the lesser-curvature side of the stomach. The gall-bladder did not look badly. He made an uneventful recovery, and gained 30 pounds during the next six months. Eight months later he had a severe attack of cholecystitis. Following this attack the X-ray showed a 20 per cent six-hour barium residue in the stomach. Cholecystectomy and gastroenterostomy were performed under local and splanchnic anaesthesia. The patient made a perfect recovery and is symptom free.

Case 2: Family history negative. *Complaints:* (1) Loss of weight, general weakness, cough. (2) Pain in back. (3) Enlarged lymph nodes. (4) Gastric distress and repeated attacks of pain in the right upper quadrant. During the last three months the pain has been more severe, with inability to take food and consequent loss of weight. The patient is a bed case. *Diagnosis:* (1) Pulmonary tuberculosis, chronic, arrested; (2) tuberculosis of cervical and axillary lymph nodes; (3) tuberculosis of lower dorsal vertebrae; (4) cholecystitis, subacute. Cholecystectomy was performed under local and anterior splanchnic anaesthesia for ulcerative cholecystitis. The stomach and duodenum were found normal. The appendix was not examined because the patient was such a bad surgical risk. One year later the patient had an acute attack of appendicitis for which the appendix was removed under local anaes-

thesia. Convalescence was normal, and the patient has since gained about 15 pounds. He has been discharged from the hospital wearing a brace for his Pott's disease.

Case 3: Mr. D., age 30 years, widower, engineer. Family history negative. Previous history negative. *Present Complaint:* The patient has had repeated attacks of pleurisy. He complains of loss of weight and strength for three years and cough for three years with recent bloody sputum. *Diagnosis:* Pulmonary tuberculosis, active. *Progress:* While under management he suffered severe constipation, distress after eating, and frequent attacks resembling cholecystitis or appendicitis. The X-ray and laboratory examinations were negative. *Operation:* Under local and anterior splanchnic anaesthesia the gall-bladder, stomach and duodenum were found normal. The bowel and mesenteric lymph nodes were free from tuberculosis and a badly diseased appendix was removed. The patient returned to bed with normal pulse, and convalesced rapidly. He is much improved, and free from constipation and distress upon taking food. His cough is improved, and he has gained 22 pounds.

CONCLUSIONS

1. Institutions for the care of tuberculosis patients should have physicians available who are trained in the treatment of nontuberculous disease.
2. Nontuberculous disease often complicates tuberculosis.
3. In our experience patients with tuberculosis stand surgical operations under local anaesthesia very well.
4. Operation should be decided upon by consultation.
5. Local anaesthesia in the writer's opinion is the method of choice, and has been sufficient in nearly 100 per cent of his cases.

THE WORKING CAPACITY OF THE TUBERCULOUS[1]

GRANT THORBURN

The time ultimately arrives in the life of all patients who have successfully waged a fight against "consumption" away from home, when they must leave the protecting walls of the sanatorium or hospital, and return to their family and household. This particular stage in the course of the patient's fight against the disease is of the utmost importance and is fraught with considerable danger. If the patient continues the "cure" and remains well, he becomes an asset to himself, his family and the community, even though he earns but a moderate wage. If, on the other hand, the disease becomes reactivated, he returns to his previous unfortunate status of incapacitation and is a distinct liability.

The successful continuation of a "cure" affects all the phases of anti-tuberculosis effort, the incidence, morbidity and mortality of the disease, through the patient and his contacts. It is of the utmost interest to the sanatorium and its staff, through its effect on the end-results of their treatment, as well as to the clinician or clinic doctor, who is watching and advising the patient; but it is of moment primarily to the patient himself, whose relapse is accompanied by a greater or less spread of the disease and the development of constitutional symptoms, to the immediate family of the patient who may be dependent upon him, and finally to the community as a whole.

The group, that meets this question at first hand and every day, comprises the clinician in private practice who treats tuberculosis, the doctor in tuberculosis clinics, the family physician, and the medical officers of industrial houses and corporations, for it is to them that the patient returns following his treatment in an institution. They must advise the man or woman in regard to work, and watch them, and assume the responsibility of their health after the disease has reached a stage such that they can be allowed to leave the institution.

[1] Presented before the Clinical Section at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 26, 1927.

We all know that pulmonary tuberculosis is a relapsing disease. Many times the patient's stay in the sanatorium or hospital is all too short, and, on entering the institution with the disease incipient or moderately advanced, he may remain only long enough for the disease to be halted and the symptoms ameliorated, and then return to his former environment and attempt to take up his previous occupation with the disease only patched up and his confidence in himself very seriously impaired. He is likely to lose confidence, not only because of his disability and relative inactivity while curing, but also his mental uncertainty as to his ability to earn sufficient to enable him to carry out the directions given by the sanatorium doctor on his discharge.

We have found that very frequently when patients are leaving a sanatorium, they are instructed, if instructed at all in regard to their future course, to rest at home for a month or two, and then look around and get a "light job," part time at first, and to eat good food, live in a room with good ventilation and sunlight (several windows are suggested, and an outside room preferable), and, above all things, not worry. In the stress and strain of modern life, with its competition in the trades, skilled and unskilled, that is a pretty full bill for the average partially disabled individual to meet. Tuberculosis is a permanently disabling disease, and, though the degree of disability may be relatively small in the case of a good clinical result with an early lesion, nevertheless the disability is there; and, with few exceptions, the people that get well and stay well realize their limitations and live accordingly, even though they work and work hard. Indeed, they often accomplish more than many nondisabled people.

If the patient has means or his own business, or is a valued member or employee of a business firm, his path may be relatively easy. But most patients of the free or moderately priced sanatoria are not so situated. They return home with savings gone, and in debt to friends and relatives, and they have no other choice than to get out and earn money with little regard to the type of work they obtain. Such a patient may have gained considerable weight and appear well, but his lungs frequently show a moderately advanced lesion in a quiescent state. His actually healthy appearance often works very seriously to his disadvantage; the generosity and patience of his family and friends may be turned to disgust and criticism; and his earnest desire and effort to stay well, take

care of himself, continue his cure and accept only suitable work, may all be attributed by the unknowing to laziness and shiftlessness. Women of this type frequently go into domestic service or take care of children to earn their living.

This group of people certainly need some attention; and, realizing this, the New York Tuberculosis and Health Association felt that a study of industry, available selected jobs and the effect of intensive vocational and medical supervision was well worth while. The Association also planned to gain some information as to work available for these cases in the city, and to keep track of their physical condition and see whether they would "stand up" better than those not supervised, and whether, by so doing, we could diminish the liability of the patients to relapse, which we believed to be high. We also hoped to work out some index or classification of the individual's ability to do selected work, bearing in mind the example of the successful classification of the New York Heart Association.

Under a decreasing donation from the Laura Spellman Fund, a three-year program was worked out, and a highly organized vocational, medical, and social-service after-care department, known as the "Vocational Bureau," was formed. Careful records were kept of all cases handled in the three years, complete medical examinations were made, and the patients were examined before being sent to a job, as well as while waiting for a position and after securing it. To do this, evening clinics were held, and painstaking case work, home visiting and social service were done on all cases. A complete and detailed study of this work will be published later.

This afternoon we shall only briefly mention a few of the interesting conclusions that we drew from our observations and from efforts to get work for, and keep at work, over 1,000 cases that applied to the Bureau, of which 676 were included in the above study. I shall also give my personal views, based on my experience with the Reco Shop, and observations from my own practice.

In the first place it would be well to say that, as far as "part-time" work is concerned, it is usually impossible to procure it for a patient, and, if it is obtained, it pays so poorly as to be of but little help. There are a few exceptions in some stores and offices, where occasionally there develops a demand for a part-time worker, but usually

the stores need this aid only in holiday season, when the crowds are so great and the air so bad that we could not make use of these positions. For a small group there are places in part-time work under medical supervision in the garment industry in the very excellent and successful Altro Shop, of which we all think so highly. Part-time work can now be obtained also for specially selected cases, if patients are willing to live in the colony at the Potts Memorial Hospital at Kingston, but further than this it is really impossible to find a four or five-hour-a-day position for anyone, except it involves the care of children or food handling, neither of which we approve. Another common fallacy, so firmly established in the minds of the laity and concurred in by many physicians, is the advisability of these ex-sanatorium patients taking up outdoor work, even though all their previous work experience has been with indoor occupations. It would seem unnecessary to emphasize that it is well-nigh impossible for a partially disabled man to enter a new field of endeavor, in which he has had no experience and which necessitates either manual labor or undue physical exertion and exposure to the elements. It is far better for the clerk to return to his desk, or the teller to his window in the bank, and devote his nonworking hours to open-air curing in his room at night or week-ends. These people stay well and, like many of you, we see many of them who return to work and maintain their disease in its inactive state. It is impossible to fit a square peg into a round hole, and it is usually as hard to make a poor chap, who has been a clerk or a student, into a farmer's helper, a horticulturist or a poultryman. In selecting work for the tuberculous, one must take into consideration not only the patient's disease, but the other members of the community or organization in which he works, as well. It is true that our patients were sputum-negative at the time of their undertaking the particular jobs that we procured for them; but we found that, of the patients who consulted us, regardless of what their diagnosis was at the time of their discharge from the sanatorium, approximately 50 per cent (343) were diagnosed as quiescent (31 per cent as moderately advanced, quiescent); and we felt that many of them might show tubercle bacilli in their sputum at subsequent examinations. We watched this carefully, and examined the sputum once a month. There were 40 per cent in the 1st stage, 50 per cent in the 2nd stage and 10 per cent in the third or far-advanced stage.

This is the type of patient that comes to the clinic or vocational bureau for guidance. They are permanently disabled; although it is true that their disability is partial and that its degree diminishes in direct proportion to the length of time they stay well and to the increasing confidence and strength they develop as time goes on and they are able to continue working.

For these patients we therefore banned work of a heavy manual type, such as dusty trades, grinding or polishing; or work that necessitated considerable physical exertion, such as soliciting, collecting, food-handling; or work in contact with children; or positions that brought the patient in close personal contact with the customer, such as barbering, manicuring, etc. However, the picture is not as black as it would seem from the above formidable list of inadvisable types of work, for each case has to be determined individually, and many industries that at first glance do not look at all promising may have one or a few positions that a patient can fill. The more intelligent the patients are, the easier it usually is, unless their intelligence is accompanied by a much higher wage requirement that may not be possible to obtain. In the work of the Bureau, we were influenced by the fact that, as this was an experiment by a public-health agency, we were obliged to make doubly sure that our placements were in work that was especially suitable for the tuberculous. We feel, however, that the actual work or type of work assumes entirely too much importance for the average inactive tuberculosis patient, and that the real factor that influences his disease is what he does when he is not working. Suitable positions for these cases can be found in almost any industry, but to get them money enough to enable them to eat well, and rest sufficiently and enjoy good living conditions is difficult to attain.

I should like to quote a few examples of positions that might seem suitable until all factors are taken into consideration:

First: Keeper of a news-stand at elevated railway stations looked promising until we found that the man had to handle cartons of candies and newspapers in bulk, which frequently required the lifting and carrying of 75 to 100 pounds.

Second: Cabinet-making looks good, if a man is a union man, but a nonunion patient may have to work 9½ hours a day and do heavy work in a shop.

Third: Watchman of building-construction seems to be a rather easy job. But when we find that, as the building rises from the street, the watchman must go to each floor by means of a ladder every hour, we see that, before the building reaches the smallest proportions of a sky-scraper, he is engaged chiefly in climbing up and down ladders all night like a veritable monkey,—certainly not a sedentary position by any means.

I could go on in this way for many other types of work; but what we did do was to try to use the men's previous training and ability, and place them into an organization where the employer was sympathetic, and in a type of work that was noninjurious. We placed them as fountain-pen chasers, radio assemblers, office clerks, salesmen, handymen, wrappers and labelers, elevator operators and salesmen; also in clerical and nursing positions in sanatoria.

The group of patients that consulted us came from all classes: 53 per cent were foreign-born, scattered among 33 nationalities, and 47 per cent were native-born. We had 75 per cent manual laborers, 18 per cent clerical workers, and 7 per cent in professional groups. They were about equally divided as to skilled and unskilled workers. Of this group 11 per cent had completed high school, and of these more than half had had some college education, while those who had not finished the grade-schools totalled 40 per cent. This is certainly a mixed group, and proves the statement that the people who need this vocational and medical advice and after-care are from the rank and file of our city population.

In looking up the previous history of our applicants in their relation to the relief agencies, we found that 76 per cent had no record of ever having had any financial help from charitable or relief organizations. This, then, is a group of people who had been fighting their battle themselves, with the aid of their families, relatives and friends; and surely they are a worthy type to help with opportune advice and counsel, of which they need so much. Only 395 (58 per cent) of these patients were under periodic medical supervision before they came to us.

Now, what did we do with these cases as far as their tuberculosis was concerned? We were able, to our great satisfaction, to get 449 of the total of 676 patients who consulted the Bureau to return for a comparative and final examination after a period of from three months to three

years. We found that 42.5 per cent remained the same, 33.3 per cent improved, and 24.2 per cent retrogressed or died. Of all our cases, 17 per cent had a definite reactivation during the three-year period. In the Reco Shop, over a four-year period, we had a 13 per cent reactivation in about 400 cases, but the cases there were earlier and more carefully selected. In the Vocational Bureau we accepted for trial any case that was inactive and sputum-negative, frequently being influenced by the urgent financial need of the patient and his family.

We also compared two groups of patients: first, those who had been under the medical and vocational supervision of the Bureau for a year or more, totalling 80 patients, and, second, as a control we compared 39 patients who had been under our observation less than a month, but in whom (like group 1) the period of time between the first and final examinations was one year or more. (The two groups were unselected as to stage or condition of disease except that no active disease was included.) These two groups are therefore comparable, except that one was supervised and the other was not. We find that the supervised cases showed 35 per cent more patients whose disease was the same or better then those unsupervised (this, of course, is based on a small number of cases).

Another point that we should like to call attention to is that, in placing these patients at work, tuberculosis was not the only disability that we had to contend with, for many of them had eye, ear, throat, or skin trouble, or deformities, all of which complicated their pulmonary condition. One hundred and eighty-one patients had one complication, and 189 had two, 161 three, 45 four, and 14 five or more complications. Needless to say, it is rather difficult to find suitable positions for a man with five, six or seven complications added to his original tuberculous disability. We had only 15 cases of complicating tuberculous laryngitis. We had 220 with visual defects, 161 with ear trouble (31 marked), and 24 with heart disease. Fifty-nine had mental symptoms, twenty-one of whom were definitely diagnosed by a psychiatrist. The orthopoedic cases numbered 56, of which 21 were tuberculous. We included 676 cases in the study, but we did not accept 74 because we considered their disease active, and we referred them back to the clinic or institution for further care. We found that 44 were nontuberculous. We had final or comparative examinations on 467 (18 were nontuberculous), so that we have 449 for

comparison. Seventy-nine per cent were under observation for over six months, and 54 per cent for over a year.

In the cases of incipient disease, 172 in number, 66 remained the same; in 65 the stage of disease remained the same and the condition improved (131 stayed the same or improved); in 7 cases the disease advanced; in 9 the condition remained the same or improved; and in 34 cases there was a change for the worse in both disease and condition.

The moderately advanced totaled 222 cases. In 99 the diagnosis was the same on the final as on the original examination; in 51 the stage of disease remained the same but the condition improved; in 9 cases the condition was the same or improved and the extent of involvement less, while in 12 the disease and condition both improved (in 173 the condition was the same or better). Forty-nine patients proved to be worse either in condition or in amount of involvement at the time of final examination.

Of the advanced cases, 37 in number, 21 stayed relatively the same, in 9 the disease was the same or less in extent, and the condition better, and in 7 definitely worse. Seven patients died. To recapitulate: 75.8 per cent of these patients remained the same or improved, and 24.2 per cent grew worse or died.

In 28 cases the lesion diminished in extent, in 339 it remained approximately the same, and in 64 it increased.

Of the 172 incipient, first-stage, quiescent cases (50 in number), 26 became arrested. Thirty-one first-stage arrested cases entered the Bureau, and 26 remained as before. Of 129 quiescent cases, 5 became arrested.

We find therefore that we had 149 cases that remained arrested or became arrested while under our observation. When we realize that we had only 17 per cent of reactivations, we feel much encouraged with the results from the standpoint of the disease.

We all know that the inactive tuberculous can work; but the object of the above was to see how well they could work, and what they could do most successfully, and also whether by careful supervision (and it stands to reason that the hypothesis is sound) we could not materially diminish their liability to breakdown. We feel that a program based on the above can and will work successfully, and have a distinct tendency to aid the returned sanatorium patient in continuing his hard-earned health.

We also feel that, finally, a distinct forward step would be marked by working out some definite, tangible classification of working ability, to be used in the reference of patients by the physician to the case-worker or nurse or personnel-worker, who is attempting to get a job for the individual. If, through usage, this scheme was found practical and the clinic doctors and clinicians and sanatorium physicians became familiar with it, the position could be sought with a much greater degree of confidence by the case-worker and the applicants placed in positions with more success.

Our idea, and we carried it far enough to draw it up and publish it, was subsequently used by a clinic in one of the large cities,—we understand with success. It aimed to classify the tuberculous employee into three groups with subdivisions (very much like the successful cardiac classification), in which it was clearly shown whether the patient was considered suitable for (1) full-time work; (2) standing or sedentary full-time work near home (eliminating the very fatiguing and trying journey to and from work, which in our city is usually spent standing up and edged in between many other people in one of our systems of transit); and finally (3) a part-time classification was put in, although I am frank to repeat that we consider the part-time jobs in industry as elusive as the will-of-the-wisp.

We believe, and we say it in no sense as a criticism of the sanatoria, realizing as we do the demands on the physician's time by his routine and emergency work, that, if more occupational therapy, shop-training and work of a nature that would increase the patient's ability to exercise and stimulate the ambition were done, we would be able to get these patients back to work more readily and with a considerably better chance of their being able to "carry on." Enforced idleness, and prolonged bed-rest, followed by a little ten-minute walk, which may before discharge be worked up to one hour, morning and afternoon, are not a sufficient foundation for us to build on, to get patients back to seven or eight-hours-a-day work, in addition to regaining their self-confidence while returning to their business and their home environment. We are forced to build up these patients' exercise in the city, in the hard and uninteresting streets, in order to get them stabilized and strong enough to return to their positions.

We believe that this problem of after-care and work is one of the most

urgent questions that we face in our efforts to get the better of tuberculosis; for it is of little avail to build institutions, to increase beds and to segregate the tuberculous for treatment, taking them away from their homes and families, if you have no further final constructive routine for them to follow when the progress of their disease is halted and their symptoms cleared up. The cities, towns and counties must realize that these patients cannot compete with healthy competitors, and that provision must be made to minimize their chances for relapse, and an opportunity given them to earn something and maintain the esteem of their friends and relatives and their own self-respect.

ERRORS OF OMISSION AND COMMISSION IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

EDWARD N. CHAPMAN[1]

How conscientiously is the medical profession using the methods at its disposal for the diagnosis of pulmonary tuberculosis?

In an attempt to answer this question partially, a large number of patients was interviewed by the author in several of the sanatoria of Colorado Springs, Colorado, during the winter and spring of 1927. It was felt that a survey of cases at Colorado Springs would give a very fair cross-section of conditions in the United States as a whole, since individuals from every section of the country are included in the group interviewed. All levels of intelligence and financial condition are represented. However, the average is probably somewhat above that for state institutions. Each patient had at least a speaking knowledge of the English language.

No attempt has been made to classify the individuals according to the stage of their disease at the time the diagnosis was made, for too large a proportion had been under treatment elsewhere before coming to Colorado. Only undoubted cases of pulmonary tuberculosis were used, and only patients who had received their initial diagnosis of tuberculosis since 1920 were chosen, for it was felt that it was asking too much of the memory of the average patient to go back for details of examination more than six years.

Each patient eligible was given a list of questions to ponder and answer. A few days later each question was gone over with the patient, and necessary explanations and corrections made. This personal interview was found to be indispensable, for almost every individual had misinterpreted at least one question. All patients whose memory seemed at all defective were eliminated, and all the reports from one large institution dealing exclusively with insurance cases were thrown out when later it was found that two or three patients, who had obtained their insurance following the discovery that they had tuberculosis, had falsified their

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statements through fear of detection. Only 200 patients, out of a possible group of five or six hundred, were considered to have met all the requirements after these eliminations had been made, and it is upon their reports that this statistical study is based.

PRESENTING SYMPTOM

Each person was asked what symptom it was that finally made him seek medical advice. The answers were as shown in table 1.

TABLE 1

	NUMBER OF CASES	PER CENT
Cough	46	24
Fatigue (rundown, malaise, lack of "pep")	46	24
Chills and fever ("flu," grippe, pneumonia)	25	12.5
Pain in chest	21	10.5
Spitting of blood	17	8.5
Colds (severe or persistent)	17	8.5
Hoarseness	4	2
Indigestion	3	1.5
Loss of weight	3	1.5
Tuberculosis in family, pain in joints, discharging ear, each	2	1
Nervousness, night-sweats, sore throat, loss of hearing, rectal abscess, amenorrhoea, "kidney trouble," each	1	0.5

Table 1 shows that cough and fatigue were equally frequent and accounted for almost half the total. It is interesting to note in this connection that fatigue, although not the presenting symptom, was present in 78 per cent of all the cases and far outran any other one symptom.

DURATION OF SYMPTOMS

Table 2 gives the length of time symptoms were present before the patient went to a physician. One-third of the cases delayed consulting a physician two months, and one-quarter three months or over, after the onset of symptoms. Evidently a health conscience has not yet been thoroughly awakened.

TABLE 2

	NUMBER OF CASES	PER CENT
Consulted physician within one month after onset of symptoms	121	61
From 1½ to 6 months	46	23
From 6 months to one year	15	8
From one year to 25 years	14	8

NUMBER OF PHYSICIANS CONSULTED BEFORE DIAGNOSIS WAS MADE

All told, 462 physicians were consulted by 195 patients. The remaining 5 went to clinics. Table 3 gives the percentages and grouping.

TABLE 3

	NUMBER OF CASES	PER CENT
Consulted one physician	84	43
Consulted two physicians	45	23
Consulted three physicians	32	16
Consulted four physicians	17	9
Consulted five physicians	7	3.5
Consulted six physicians	3	2
Consulted seven physicians	1	0.5
Consulted nine physicians	2	1
Consulted ten physicians	1	0.5
Consulted twelve physicians	3	1.5

CHEST EXAMINATION

In 89.5 per cent, or 179 of the cases, there seemed to be enough symptoms at the time the patient first consulted a physician to warrant an immediate chest examination; that is, there were one or more of the following symptoms present: cough, sputum, pain in the chest, dyspnoea, severe or persistent cold, or a history of blood-spitting. In 10.5 per cent, or 21 cases, there were not sufficient symptoms at the time a physician was first consulted to point directly to possible pathological changes in the chest, but in 8 of these the symptoms became positive long before the diagnosis was made. Of this total of 179 cases that seemed to warrant an immediate chest examination, 81 per cent, or 145 cases, received a chest examination within a few weeks. In 12 per cent, or 28 cases, there was no examination for from 2 months to 8 years. Here are a few instances of gross neglect: One patient had no examination for eight years despite frequent attacks of pleurisy; the physician simply strapped the chest without making an examination. Another patient had frequent attacks of pleurisy for five years, but the physician consulted made no chest examination; the first who did made a diagnosis without difficulty. A third patient with positive symptoms consulted three men in two and a half years without examination. A fourth had no examination for four years; the patient was told he was run down and given tonics. A fifth had no examination for fourteen months in spite of plenty of

symptoms; a diagnosis was easily made by the first physician to use a stethoscope. One patient consulted six physicians in a large eastern city, none of whom listened to his chest in spite of his history of a number of recent haemorrhages. Another man with positive symptoms consulted a physician, who laughed at his fears of tuberculosis and gave him cough medicine without examination. Still another was treated for a cold for five months with no examination; he then went to another physician who at once found abundant signs in his chest. Three per cent, or 6 cases, had no chest examination at any time.

In only four cases did the physician listen to the chest through the patient's clothes. Three patients stated that only part of the chest was examined.

In 127 cases repeated chest examinations seemed warranted because of positive chest symptoms but negative chest signs. Of this number 64 per cent, or 86 cases, received more than one examination, while 36 per cent, or 41 cases, did not receive them.

COUGH DURING EXAMINATION OF CHEST

It should by this time be well recognized that the possibility of hearing râles during examination of the chest is considerably increased if the patient is asked to cough slightly at the end of each expiration, and inspire. Only 179 cases could answer this question, but of these 58 per cent (104 cases) were asked to cough, while 42 per cent were not. Of these 71 patients who were not asked to cough, 4 had had a recent haemorrhage, so that the procedure may have been advisedly omitted for this reason.

SPUTUM EXAMINATIONS

Every case with symptoms suggesting pulmonary tuberculosis should at least have a specimen of morning saliva examined, whether sputum seems to be present or not. The great majority of our State Boards of Health offer this aid without charge. Neglect of this simple procedure almost, if not quite, constitutes malpractice.

Of the 179 cases with chest symptoms positive when they first consulted a physician, 60 per cent (109 cases) had their sputum examined within two months. The sputum of 21 per cent (37 cases) was examined after a long delay, that is, two months to ten years, and 19 per cent (33 cases) did not have their sputum examined at all.

Of those with negative sputum on the first examination there were 46 cases. Seventy-two per cent of these (33 cases) received at least one other sputum examination, while 28 per cent (13 cases) did not receive a second examination.

TEMPERATURE RECORDS

The aid accorded by a temperature record, carefully kept for several weeks in cases in which active tuberculosis is suspected, has been repeatedly emphasized. It is, of course, of value only when abnormal; since an active lesion is still possible even though there be no elevation of temperature. I have been very lenient in table 4, and have considered that a temperature record of the case has been kept if the attending physician occasionally took the patient's temperature. As a matter of fact, a slight elevation of temperature is often missed by any such haphazard observation. I have not included the cases in which an immediate diagnosis was made.

TABLE 4

	NUMBER OF CASES	PER CENT
Temperature record kept within 2 months	52	30
Temperature record kept 2 to 6 months	8	5
Temperature record kept 6 months to 5 years	21	12
No temperature record asked for	88	53
	169	

USE OF THE X-RAY

From table 5 it will be seen that less than one-third of the patients received an X-ray of the chest within two months of the time they first consulted a physician, and that over one-third were never given the benefit of an X-ray examination at any time. When one considers that a certain proportion of these individuals come from country districts, where X-rays are not readily available, the neglect seems less censurable.

TABLE 5

	NUMBER OF CASES	PER CENT
X-ray taken within 2 months	59	30
X-ray taken 2 to 6 months	24	13
X-ray taken 6 months to 10 years	37	19
No X-ray taken	72	38
	192	

Each individual was asked why an X-ray was not taken, to which the great majority answered that "it was not suggested." A very few cases demurred at the expense.

Of the 110 given chest X-rays before the definite diagnosis of pulmonary tuberculosis was made, 30 per cent, or 34 cases, were convinced that the physician had heard no definite signs in their chests up to the time the X-ray was taken, and that the initial diagnosis rested upon the roentgenograph plus symptoms. These figures do not include 5 patients with a positive X-ray whose chests were never examined. This is, of course, the patients' interpretation of the physician's examination of their chests and may be in considerable error. In 67 per cent, or 74 cases, both the chest examination and the X-ray were positive.

The X-ray plates perhaps led the physician astray in 12 cases. These were largely errors of interpretation, such as a "spot on the lung" considered due to influenza occurring several years before; several were considered as showing entirely healed or dormant lesions in spite of the fact that the patient at the time had definite symptoms of activity; several were thought to be negative, but when the plates were seen by men skilled in their interpretation quite evident lesions were found to have been overlooked; two were diagnosed as lung abscess, and in several the lesions were considered to be thickened pleura.

TIME NECESSARY FOR DIAGNOSIS

How long a time elapsed from the day the patient first consulted a physician until he or some member of his family was told that he had tuberculosis?

TABLE 6

	NUMBER OF CASES	PER CENT
Diagnosed within 2 months	104	52
Diagnosed 2 months to 1 year	60	30
Diagnosed 1 year to 10 years	36	18

Referring to table 6 it will be seen that practically half the cases had symptoms of a more or less definite nature and had been under the care of a physician (though not continuously so in some instances) for over two months before a diagnosis of tuberculosis was made.

ERRORS IN DIAGNOSIS

Listed in table 7, in the order of their frequency, are the diagnoses given the patients before pulmonary tuberculosis was finally found to be present. Some of them are undoubtedly correct as far as they go, but in all the tuberculous nature of the disease had been overlooked, or the patient was purposely misled. I give them in the patients' own words.

TABLE 7

Bronchitis	33	Stomach cough	1
Rundown	19	Typhoid	1
Influenza	17	Intestinal "flu"	1
Pleurisy (non-T.B.)	15	Chronic ulcer of ear (non-T.B.)	1
Colds	8	Chronic appendicitis	1
Pneumonia	5	Postoperative weakness	1
Nervous breakdown	4	Sinusitis	1
Nervousness	4	Mastoiditis	1
Spots on the lung	4	Thyroid trouble	1
Throat trouble	3	Elongated palate	1
Asthma	3	Weakness	1
Bad tonsils	3	Rheumatism	1
Tonsillitis	3	Whooping Cough	1
Anaemia	3	Rectal abscess (non-T.B.)	1
Catarrh	2	Myocarditis	1
Laryngitis (non-T.B.)	2	Neurasthenia	1
Intercostal neuralgia	2	Hookworm	1
Ulcer of stomach	2	Shell shock	1
Overwork	2	Spinal meningitis	1
Weak lungs	2	Catarrh of stomach	1
No disease	1	Strained vocal cords	1
Cigarette cough	1		

PROPER ADVICE

After a definite diagnosis of pulmonary tuberculosis had been made, how many patients were given proper advice? Bed-rest is now generally recognized as the first essential in the treatment of active tuberculosis. I therefore considered advice in which rest had little or no part as improper.

TABLE 8

	NUMBER OF CASES	PER CENT
Individuals given proper advice	156	84
Individuals given improper advice	28	16

Here are a few illustrations of advice in which nothing was said about complete rest:

Take a year off
Eat three times too much
Exercise and take tuberculin (2 cases)
Take it easy (4 cases)
Play golf
Good food and fresh air
Stop work, live in a dry climate and take codliver oil
Go to New Mexico and continue working
Go to Denver
Go west and work (2 cases)
Change of climate (2 cases)
Go west (4 cases)
Go to a high altitude

Much of this advice led the patients to think that all they had to do was to breath the ozone of Colorado or the Southwest in order to cure their tuberculosis. This attitude invariably resulted in a long and sometimes perhaps a fatal delay in treatment.

INITIATION OF TREATMENT

How soon did the patient start rest treatment? This question was asked in the attempt to discover how coöperative the group of patients was in the matter of treatment, and what effect, if any, improper advice had in delaying treatment.

An early diagnosis is, of course, of little value if the individuals, many of whom often do not feel very sick, are not willing to carry out their physician's instructions, even though it may mean laying aside for the time being all that is held dear.

Referring to table 9 we find that two-thirds of the cases started approved treatment within two weeks of the time that they discovered tuberculosis was present, while by the end of one month 80 per cent had given up their work, gone to a sanatorium, or were on complete rest at home. Eleven cases were delayed from three months to six years because of improper advice on the part of their physician, instances of which I have already given. Two cases delayed a number of months because they did not believe the diagnosis, while one thought he had to earn money before starting the "cure."

TABLE 9

	PER CENT
Started rest treatment within 2 weeks	66
Started rest treatment 2 weeks to 1 month	14
Started rest treatment 1 to 6 months	13
Started rest treatment 6 months to 1 year	4
Started rest treatment 1 to 6 years	3

Fifteen of the series of 200 cases seemed to have reasonably good evidence that their attending physician had made a definite diagnosis of tuberculosis, but did not tell them of it, or else tried to mask the true nature of the disease by calling it "weak lungs" or "you have spots on your lungs," and was so successful that no suspicion of tuberculosis entered the patient's mind. The worst instance was that of a barber, who was allowed to go on with his trade for seven or eight months after a definite diagnosis had been made, because the physician was a personal friend who hated to break the news to him. During all this time he had a severe cough and was raising constantly. In addition to taking away from this man his chances to arrest his disease this misguided physician exposed many others to unusual opportunity for infection. It is easier to fight when we know what we are fighting. Uncertainty is often the most difficult thing to bear, and, if the fifteen physicians who robbed these patients of precious months of proper treatment through a false sense of friendship or kindness could hear their reproaches as I heard them, they would never be tempted to make this mistake again.

COMMENT AND CONCLUSIONS

It is difficult to compare the figures presented in this article with those found in the literature dealing with this general subject. I am aware of no recent work along these lines. Furthermore, it may be hardly fair to compare this group of patients with those entering state institutions for the reasons already mentioned, namely, because these Colorado patients represent a greater diversity of intelligence and financial ability than is usually found in a state institution, and also because they come from no one section of the country. I should estimate that roughly from one-quarter to one-third of these individuals are of a type not found in municipal or state sanatoria.

Undoubtedly improvement has occurred in the last decade in the education of the medical profession in the diagnosis of tuberculosis, and of the public in seeking intelligent advice. Such doleful figures as those of

Ford (1) based on a study, I judge, of the records of 1,000 patients admitted to Gaylord Farm Sanatorium, Wallingford, Connecticut, from 1907 to 1915, do not seem possible at the present time. Even making generous allowances for difference of type, the figures of the Colorado group show a vastly better condition prevailing to-day. Ford found that 193 physicians out of 1,940 examined the patient's chest without removing the clothing, as against only 4 out of 462 in my group, with an additional two who listened to only part of the chest. Of 741 patients with moderately advanced tuberculosis on entrance 33 per cent, or 250, had never had a sputum examination, against 19 per cent of the Colorado cases in all stages of the disease. Ford moreover found that 10.2 per cent of the physicians consulted by his group made no examination of the patient whatsoever.

The medical profession has also improved in discharging its obligation to inform the patient of his condition when tuberculosis is present. Dearholt, quoted by Hawes (2) in a study of tuberculosis in the State of Wisconsin, showed that 60 cases of tuberculosis out of a group of 195 were not told that they had the disease, although their attending physician was sure enough of the diagnosis to register the case with the Board of Health, and of 159 cases not registered 91 were deceived or left in ignorance of their true condition.

The tendency of late has been to ascribe the rapidly falling death-rate from tuberculosis in this country to improved economic conditions and a gradually developing racial immunity to the disease. These are undoubtedly significant factors. However, if it is fair to draw conclusions from the statistics of the group of patients which I have presented, it would seem that at least a little credit should go to a more enlightened and conscientious medical profession, and to those individuals and organizations that have made this possible. That there is still room for great improvement is seen from the fact that only two-thirds of the cases with definite chest symptoms were given repeated chest examinations; that only slightly over half were asked to cough during any of their examinations; that less than half were asked to keep a record of their temperature; that only 52 per cent were given at any time the benefit of our newest and most valuable means in the detection of early pulmonary tuberculosis, the X-ray; and, finally, that half the cases required more than two months for a diagnosis.

I am indebted to Drs. Forster, Giese, Harris, Ryder and Webb for valuable suggestions and their courtesy in allowing me to interview patients.

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THE X-RAY AND CLINICAL DIAGNOSIS OF TUBERCULOSIS IN CHILDREN[1]

HENRY D. CHADWICK

I feel like apologizing for again speaking to the members of this Association on the subject of juvenile tuberculosis. In 1921 I read a paper at our Buffalo meeting, stressing the need of a new classification, so that the cases of juvenile tuberculosis could be kept separate from the adult type of pulmonary disease.

Symptoms, physical signs and the prognosis of the two types of disease are so different that their separation into two distinct groups became of greater importance with the more general recognition of the childhood type of tuberculosis. Otherwise, comparative statistics covering reported cases, results of treatment and mortality from tuberculosis would, in a short time, become confused and misleading.

The report submitted by a committee on classification appointed by the American Sanatorium Association was accepted at the annual meeting held in Minneapolis. The next year a committee from the National Tuberculosis Association was appointed to revise the fifth edition of *Diagnostic Standards* and incorporate in the sixth edition a section on *Juvenile Tuberculosis*. This was done, and the name *Hilum Tuberculosis* was officially recognized as the term to be used to describe the juvenile type of tuberculosis. This name is open to some objections, but so is every other one that was proposed in its place.

In this discussion I shall use the terms *hilum tuberculosis* and *juvenile type of tuberculosis* synonymously. These terms are used to describe the disease which follows a first infection of a child's lung with tubercle bacilli. First, there is produced a primary nodule in the pulmonary parenchyma. It may vary in size from one that is microscopic to one that is a conglomerate tubercle several millimetres in diameter. It may be found in any part of the pulmonary parenchyma. Such nodules may be single or multiple.

Coincidental with the development of this nodule is the infection of

[1] Presented at a meeting of the American Sanatorium Association.

the adjacent tracheobronchial lymph nodes, which receive the lymph-flow from the region of the primary nodule. This is the primary complex first described by Ranke. Because of this association of pulmonary and lymph-node disease, the name of tracheobronchial tuberculosis does not adequately describe the condition that exists. It is open to the same objection as the term *hilum tuberculosis*, but the latter has the merit of being in current use by physicians in some of the European countries. We, of course, need not have followed their lead in this, but, before proposing a different term, we should be certain that we have chosen one that is more descriptive of the process we wish to name.

It would indeed simplify matters if we spoke of the juvenile type of tuberculosis, which is the result of a primary infection, and the adult type of tuberculosis, which is the result of a secondary infection. It would perhaps simplify our nomenclature if we gave the name of *juvenile type of tuberculosis* to the condition that follows a first infection, and the name *adult type of tuberculosis* to the condition which follows a secondary infection.

The juvenile type of tuberculosis is a children's disease sometimes found in adults, and manifests itself by a small, discrete, sharply circumscribed primary lesion, accompanied by a much greater involvement of the tracheobronchial lymph nodes.

The adult type of tuberculosis is a disease of older people, but is occasionally found in children. It is usually found as a diffuse lesion in the upper third of the lung, and there is no associated clinical involvement of the adjacent lymph nodes. Adolescence is a border-line period in which either one of the two types may be found, or the juvenile type may be found combined with the adult pulmonary disease.

The term *latent hilum tuberculosis* is used to describe the cases in which the roentgenograph shows pulmonary nodules of tuberculous tracheobronchial lymph nodes or both, but in which symptoms of active disease are absent. Because of the age of the child, we know that such tuberculous lesions are comparatively recent and, therefore, contain living tubercle bacilli. The child is in the state of equilibrium as long as the balance between the effects produced by the tubercle bacillus and the resistance to the invader are maintained. This condition may be fleeting or it may be permanent.

The element of chance as to whether intercurrent disease appears to lower resistance, the amount of rest, of outdoor life, of strenuous ath-

letics are some of the factors that determine the issue as to whether cases remain latent or become active and progressive. With these preliminary statements, we will now discuss diagnosis.

We have five factors to consider in a given case. In the order of importance, they are as follows:

1: Roentgenological evidence of calcified tracheobronchial lymph nodes or primary nodules in the lung.
2: Positive tuberculin test.
3: History of exposure to a case of open pulmonary tuberculosis.
4: Physical signs.
5: Symptoms.

1: The X-Ray: A roentgenograph is the most valuable aid in the study of these children. Without it there can be no absolute diagnosis of hilum tuberculosis as a possible cause of ill health in a child.

The work of Opie and McPhedran, of the Phipps Institute, in their studies of the lungs of children, have given us a sounder basis for the interpretation of X-ray shadows found in the lungs. They have demonstrated that enlarged tracheobronchial lymph nodes only appear as opaque shadows in a roentgenograph when they contain deposits of calcium; also that calcium is deposited in lymph nodes only when they are tuberculous.

Slight changes in area or of density of the hilum shadows are of no significance. If, however, there appear spots of increased density, with irregular outlines in the region of the normal hilum shadows or along the trachea, that have the form of lymph nodes or lymph-node masses, then we are justified in assuming such shadows to be due to calcified, tuberculous lymph nodes. Frequently when such lymph nodes are found, there are one or more calcified nodules to be seen in the parenchyma of the lung.

Rarely one finds a large area of homogeneous shadow extending from the hilum or well out toward the periphery, due to an exudate resulting from the inflammatory reaction set up by a recent first infection with tubercle bacilli. If such a case is followed by serial films taken at several months' intervals over a period of one to three years, one finds that absorption of the exudate gradually takes place, and eventually only a small, calcified nodule remains at the site of the infiltrated area.

When this exudate occurs at an apex, as it sometimes does, or well out into the periphery of the pulmonary parenchyma, then only time

will settle the question as to whether we are dealing with a juvenile or adult type of tuberculosis. The differential diagnosis in a given case is sometimes very difficult until absorption has taken place or progressive disease indicates its character.

In a recent epidemic of measles at the Westfield State Sanatorium, my associate, Dr. Roy Morgan, took serial roentgenographs of the 32 children that developed the disease while under treatment. We compared the roentgenographs taken before the onset of the measles with others taken during the course of the disease and after recovery had taken place. In no cases were there changes in the hilum shadows that appeared as enlarged lymph nodes. In some cases the hilum shadows were increased in area or density or both, but these shadows were homogeneous. No enlarged tracheobronchial lymph nodes could be seen that were not there before. When the area of homogeneous shadows was increased by the attack of measles, absorption of the inflammatory exudate took place within a month, and the hilum region was back to the condition which was present before the illness began.

In the films of children one occasionally sees enlarged trunks extending outward from a mass of calcified hilum lymph nodes, indicating obstructed channels and engorged vessels. I do not consider prominent pulmonary markings pathological when not associated with dense lymph-node masses in the hilum.

2: Tuberculin Test: We can assume in children that a positive tuberculin test indicates the presence of living tubercle bacilli. It does not tell us whether the disease is active or latent. Rarely, repeated tests are negative when definite calcified nodules or lymph nodes are found in the roentgenograph. In such cases the disease is either obsolete or the tissues of the child have, for some reason, lost their hypersensitiveness to tuberculin.

Tests that are negative in a suspected case should be repeated with increasing doses of tuberculin applied intracutaneously. In a series of 200 children, on whom we did the Pirquet test and intracutaneous test simultaneously, we obtained 10 per cent more reactors with the intracutaneous method. It is the one to be preferred when a choice can be made.

3: History of Exposure: We found in the Massachusetts State Clinics that 48 per cent of the six-year-old children said to be contacts were reactors and but 15 per cent of the noncontacts of the same age. We found that the percentage of contact children was as high at age six as

at age fifteen. These children, because of being subjected to a longer period of exposure and more massive doses of bacilli, are more prone to develop the juvenile type of tuberculosis.

FIG. 1. SUSPICIOUS CASE

Note the flocculent shadow in each hilum. This may be due to tuberculosis of bronchial lymph nodes that have not yet become calcified enough to show in sharp outline. It may be due to other infection than tuberculosis or to passive congestion, the result of cardiac disease. A positive diagnosis is not possible in such a case. When, however, a child reacts to the tuberculin test, is in poor general condition and has a roentgenograph showing such hilum shadows, and no other cause is evident, then it should be considered as probably tuberculous.

FIG. 2. HILUM TUBERCULOSIS

Calcified lymph nodes in left hilum. No other evidence is needed to make a positive diagnosis. Such a case might be without symptoms, and so might be called latent, but if under 18 or 20 years of age should be carefully supervised, as living tubercle bacilli are usually present in these lesions.

FIG. 3. HILUM TUBERCULOSIS

A large calcified nodule shows in the 5th right interspace. The right hilum shows calcified lymph nodes that have become diseased as a result of infection carried by the lymph-stream from the primary focus.

FG. 4. HILUM TUBERCULOS IS

This shows a type of juvenile tuberculosis in which a large area of shadow is seen extending out from the left hilum. This is due to congestion about a mass of tuberculous lymph nodes recently infected. In a few months it will become much smaller in area, and in two or three years a small calcified mass will be all that remains. In some cases complete absorption takes place and nothing remains to show that there has been any lesion.

FIG. 5. HILUM TUBERCULOSIS

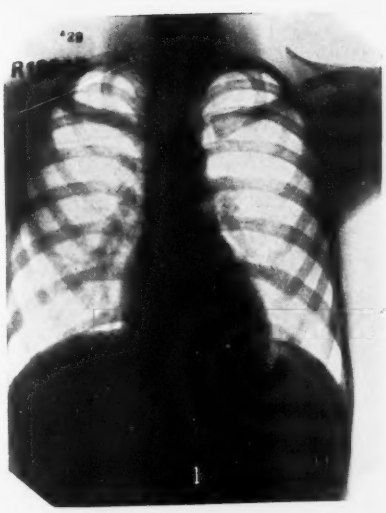
This shows a perifocal congestion about a recent primary lesion. In a few months to a year, absorption of the exudate takes place and leaves a small nodule, which eventually becomes calcified or in some instances may be entirely absorbed.

Such a case at this stage of the disease does not show much hilum involvement and therefore would more appropriately be called the juvenile type of tuberculosis. In course of time, however, the parenchymatous lesion becomes insignificant and the hilum lesion more prominent.

FIG. 6. BLOOD-VESSEL SIMULATES CALCIFIED LYMPH NODES

In the right hilum between the 5th and 6th ribs posteriorly is a round dense spot and beside it is a bronchus in cross-section. Such round or oval spots with regular outline and usually accompanied by a bronchus should not be mistaken for a tuberculous lymph node.

In the analysis of 25,000 school children examined in our clinics, we found four times as many cases of hilum tuberculosis and twice as many cases of pulmonary tuberculosis in the contacts as were found in the noncontact group.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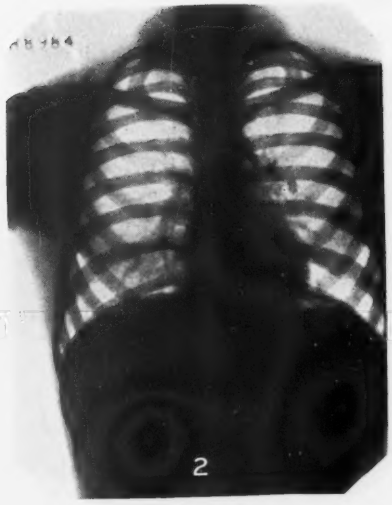
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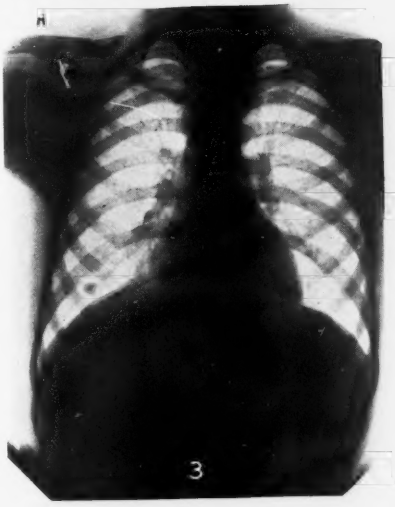
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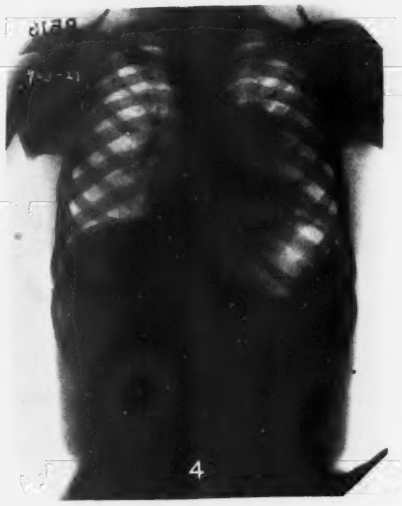
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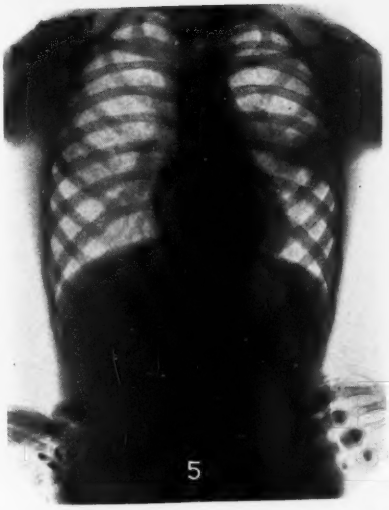
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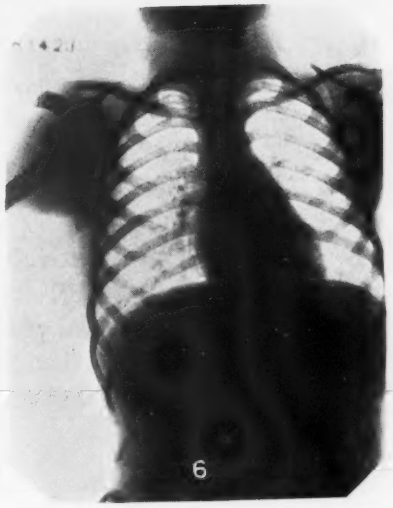
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4: Physical Signs: There are few physical signs indicative of juvenile tuberculosis. There are none that are pathognomonic. It is true that in an occasional case sometimes one may find definite interscapular dulness. This is probably the result of muscular spasm, due to inflamed mediastinal lymph nodes. I do not find the D'Espine sign of any value. Auscultation and percussion are important only as they may determine the absence or presence of any other diseased condition.

By physical examination alone the most skilful examiner cannot make a positive diagnosis of juvenile tuberculosis; neither can he exclude it as one of the possibilities, regardless of the physical appearance of the child.

Pleurisy with effusion is one of the conditions that must be considered among the physical signs of juvenile tuberculosis. In our school clinics, out of 8,838 X-ray films we found 12 children with pleuritic effusions, 9 at the right base and 3 at the left. Three other roentgenographs showed adhesions in the costophrenic angle. Of 2,100 children, from three to seventeen years of age, that have been under treatment at the Westfield State Sanatorium since we made use of the X-ray as a routine procedure, we have found 46 with pleuritic effusions. In these cases we were unable to find any pulmonary involvement of the adult type. It is our experience that these effusions absorb rapidly with rest treatment and leave no adhesions or visible thickening of the pleura.

When we remember that the primary lesions are usually subpleural, we can understand why we find these effusions in children with the juvenile type of tuberculosis. It is probable also that the effusions in adults, without apical involvement, are also caused by the pleura becoming infected from the primary focus that may have been present for years. Such a pleurisy may be a reactivation of a latent juvenile type of tuberculosis. If this is true, then we should not continue to classify adults having pleuritic effusions as cases of the minimal type of pulmonary tuberculosis, unless they also have parenchymatous disease.

5: Symptoms: Undue fatigue, nervous irritability and frequent colds are the most common symptoms noted in these cases. When found in children that have pulmonary nodules or tracheobronchial lymph nodes, we should consider the disease active. Fever over 100° in these children is unusual, unless pleurisy with effusion develops, and in such cases the temperature may go up to 101 and 102°, but after a few days becomes normal. With these cases of pleurisy there is no complaint of pain. It is one of the possibilities that should always be considered whenever a child has a febrile attack that cannot otherwise be explained.

Malnutrition does not appear from our studies to be a predisposing cause of tuberculosis, but when it exists it may be the result of tuberculous infection. Symptoms, such as I have mentioned, are an index of the activity of the disease. They are not to be considered an important factor in diagnosis.

SUMMARY

A diagnosis of juvenile tuberculosis can only be made from a study of the roentgenograph. We are on safe ground if we classify as tuberculous all tracheobronchial lymph nodes and pulmonary nodules that show evidence of calcification. As McPhedran has pointed out, we must not be deceived by the circular or oval densities, due to blood vessels caught in the same axis as the ray. Close beside these spots are often seen the accompanying bronchus in cross-section outline. They are often found near the hilum in the fifth interspace posteriorly. Similar vascular spots are occasionally seen along the descending right bronchus.

The cases in which hilum shadows are considerably increased in area or density, but do not show definite lymph nodes or lymph-node masses, should be considered as suspects. These suspicious cases, if they are found to be reactors, and have symptoms indicating activity, should be given as careful supervision as those with a positive diagnosis. Such cases may have tuberculous lymph nodes undergoing caseation, but no deposit of calcium has, as yet, taken place. They are not dense enough to be visible in the normal hilum shadows. Then again, the diseased lymph nodes may be behind the sternum or obscured by the heart shadow. The primary lesion may be too small to see, or be hidden by the ribs or dome of the diaphragm. Only in a small percentage of the children that have juvenile tuberculosis is a positive diagnosis possible. Again let me repeat that a positive diagnosis of hilum tuberculosis should not be made unless evidence of calcification is seen in the tracheobronchial lymph nodes or primary nodules in the lung.

Others with doubtful shadows at the hilum, or extending out from it, should be classified as suspicious. The ratio of suspicious cases to positive ones will be about three to one. The positive cases, as indicated by the deposit of calcium, have shown a tendency to heal. The suspicious cases, for lack of elapsed time or some other reason, have not as yet demonstrated their ability to protect themselves from the tubercle bacillus. This group of suspicious cases, therefore, should be kept under observation and receive intelligent treatment until sound health is assured.

RÂLES IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS[1]

FRED H. HEISE

Auscultatory physical signs have always played an important part in the diagnosis of pulmonary tuberculosis from the time of Laennec's discovery and development of them. Until comparatively recently, less than twenty-five years ago, they were the only means of verifying an existing pulmonary lesion in the absence of a positive sputum. More recently the X-ray has given us increased facilities in studying the normal and abnormal variations in the anatomy of the chest and a very comprehensive idea of any pulmonary pathological condition. As increased use of the X-ray has led to a fuller interpretation of its value in diagnosis, the necessity of revising our standards of diagnosis and classification naturally came about. With this increased knowledge very often substantiated by autopsy, physical signs were looked upon as of far less importance than heretofore, so that now it is not amiss to attempt to evaluate various physical signs in diagnosis.

Before the advent of the general use of the X-ray in the diagnosis of pulmonary disease, more and more emphasis was laid upon the need of discovering early any abnormal physical signs in the chest, so that, when present, tuberculosis might be treated at once with the greatest chance of satisfactory recovery. This naturally led to ultrasensitive and critical standards for interpretation of breath-sounds and adventitious sounds and also of impairment of resonance. As a consequence, we know now that quite a few patients were erroneously diagnosed as tuberculous. Many were stigmatized to their individual loss, both socially and financially, and others were refused protection by insurance. We now know that the normal variations in physical signs are broad for both percussion and auscultation, so that minor changes from the previously taught normal are not considered as seriously in diagnosis as formerly.

Some time ago it was shown that such minor changes in breath-sounds as prolonged expiration, slight bronchovesicular breathing and increase of vocal resonance and slightly distant breathing, were very frequently

[1] From the Trudeau Sanatorium, Trudeau, New York.

found in individuals with no pulmonary disease (1). At this time the value of râles in diagnosis was substantially emphasized. Their presence is easy to detect, and they are least likely to be influenced by personal interpretation. Are they wholly satisfactory for diagnosis? Can one rely implicitly on them for diagnosis?

As everyone knows, it is of most importance to begin the treatment of pulmonary tuberculosis as soon after the beginning of the lesion as is practicable. In other words, the detection of the lesion in its minimal stages is most important if treatment is to be followed by a satisfactory result. For, other things being equal, the more advanced the lesion the less favorable the outlook for recovery or for restoration of working ability.

Do râles occur with sufficient frequency in minimal tuberculosis for us to say that pulmonary tuberculosis is present or absent according to the presence or absence of râles? This is unquestionably an important thing to decide. To determine this question for personal satisfaction an analysis was made, to see just how reliable for diagnosis the occurrence of râles might be. A total of 1,877 tuberculous individuals were examined for entrance into Trudeau Sanatorium. All diagnoses were confirmed after complete examinations. The presence or absence of râles was noted upon their initial chest examination at Trudeau.

There were 351 minimal cases, almost all of which had definite X-ray changes, but only 145, or 41 per cent, were found to have definite or questionable râles upon first examination. More than one-half (59 per cent) had no râles. In that stage of pulmonary tuberculosis most amenable to treatment and of most value to detect, râles were absent in more than one-half of the subjects examined. Certainly it cannot be gainsaid that the absence of râles should not be used as the sole criterion for the absence of pulmonary tuberculosis. If in no other way the value of the X-ray for the diagnosis of pulmonary tuberculosis can be shown, it would nevertheless be true that in the detection of early pulmonary tuberculosis stereoscopic X-ray films should always be taken. However, for nontuberculous pulmonary diseases this does not always hold true.

When 1,299 moderately advanced cases (classification of 1922) were considered, it was found that 980, or 75 per cent, possessed râles. About one-fourth would have missed diagnosis had the occurrence of râles alone been the criterion of diagnosis. For far-advanced cases the râle might justly be used, for in 203, or 89 per cent, of 227, râles were found.

But even here it can justly be said that the X-ray will give a much better or more complete diagnosis than the ear.

Another interesting fact brought out in this analysis was the lessening in the number of those in whom râles could be heard upon the initial examination at Trudeau in the minimal, moderately and far-advanced groups in the more recent years. (All cases used in this analysis, entering Trudeau before the adoption of the present classification, were reclassified.)

Of the 232 minimal cases entering Trudeau between 1915 and 1921, 111, or 49 per cent, had râles, whereas of the 119 entering between 1921 and 1925, only 34, or 29 per cent, had râles. This in all probability, as thought by Dr. Lawrason Brown, is a reflection of the fact that in more recent years, with the use of the X-ray, the minimal cases without râles are being diagnosed more frequently, whereas formerly they were classed as nontuberculous or were diagnosed as tuberculous at a later stage.

The variation in the moderately advanced group was equally as great. Of 723 of these entering between 1915 and 1921 râles were found in 606, or 84 per cent, whereas in the 576 entering between 1921 and 1925 râles were heard in 374, or 65 per cent.

In the far-advanced group practically no variation occurred in the different periods; 90 per cent and 89 per cent, respectively, of 129 and 98 cases had râles.

There has been no great variation in the number of patients having positive sputum between the two periods, 1915 to 1920, and 1921 to 1925 inclusive. In the first period tubercle bacilli were found in 32 per cent of minimal cases and in the second period in 26 per cent. For the moderately advanced the figures were 63 per cent and 57 per cent respectively; somewhat of a decline (6 per cent) as the years have gone by, but not marked.

RÂLES IN THE PROGNOSIS OF PULMONARY TUBERCULOSIS[1]

FRED H. HEISE

After râles have been found and the diagnosis of tuberculosis has been made, the problem next arises in the course of treatment whether the patient is improving or getting worse. It would be very simple if improvement in the foci of disease were to go hand in hand with diminution in the number of and the area over which râles are heard, and *vice versa*. Does this actually occur, however? We do know that, when gross changes for better or worse have occurred, there are usually changes in physical signs, and especially râles, which manifest themselves usually at a later date than the immediate onset. And frequently after an acute symptomatic setback, when the patient again feels much improved, changes in the number, the character and the area of râles are found. However, for the more complete and exact treatment of the patient, it is desirous of knowing when changes for the worse are beginning and not after they have occurred. Therefore, detection of minor changes become of importance. Physical signs, to be of value, should show minor changes with a sufficient frequency to warrant the statement that, as they become more marked or less marked, the patient likewise becomes worse or better. Unfortunately, except grossly, this does not seem to occur.

There are many reasons of physics why such an ideal situation does not always occur. Just why the fact holds true in any one instance is difficult to say. We do know, however, that the X-ray usually reveals much more intensive processes than physical signs. It is questionable whether more than 20 per cent of all cavities are distinguished by physical signs. At times even superficial cavities of large size cannot be demonstrated by physical signs. The same reasons of physics governing these facts also govern the detection of râles. It is a matter of fact in the experience of many practitioners that changes in physical signs, and especially râles, do not always follow changes in the foci of disease, though they do at times.

[1]From the Trudeau Sanatorium, Trudeau, New York.

How often do the changes in râles run parallel to the changes as seen upon the X-ray film? Can one rely upon changes in râles to prognosticate? Four hundred and twelve records were gone over to see what reliance could be placed on the changes in râles as checked by changes in the X-ray film. In the course of six months the râles remained the same as to area and character in 111, of which 103, or 93 per cent, showed definite X-ray improvement, 2, or 2 per cent, X-ray relapse, and 6, or 5 per cent, a stationary condition in the X-ray.

From this it can be said that when there is no change in area or character of râles, the chances are overwhelmingly in favor of the patient having shown improvement otherwise. The danger of relapse having occurred is very small.

Râles were found over a greater area in 92 patients; yet of these, 65, or 71 per cent, showed X-ray improvement and 5, or 6 per cent, a stationary condition. In this group 22, or 23 per cent, showed X-ray increases. It is obviously not as safe to say a patient has improved in spite of increasing râles, since one in four are worse. Nevertheless more show improvement with increasing râles than show relapse.

In 83 patients the râles showed diminution of area. Most of these, 73, or 88 per cent, likewise showed X-ray improvement and only 5, or 6 per cent, relapse; and 5, or 6 per cent, a stationary condition by X-ray. Under these conditions it can be said that it is fairly safe to presume that when râles decrease in area the patient is improving. The same thing can be said when râles actually disappear. Of 75 such instances X-ray improvement was shown in 62, or 83 per cent; relapse in 2, or 2 per cent; and a stationary condition in 11, or 15 per cent.

In 51 patients râles were found after treatment and not before. Of these 40, or 78 per cent, showed X-ray improvement; 3, or 6 per cent, relapse; and 8, or 16 per cent, a stationary condition.

When râles decrease or disappear the X-ray shows likewise an improvement, so that the changes are more or less parallel. However, when râles develop or increase in area this does not hold true, for more than three-fourths of such instances are accompanied by improvement or a stationary condition in the X-ray. In only one in four instances is the patient worse. Nor is it substantiated by fact that râles, which do not change over a period of time, mean an unchanging focal condition as determined by the X-ray. The vast majority of such patients undergoing treatment show actual improvement in the X-ray film (93 per cent).

A PATHOLOGICAL STUDY OF X-RAY SHADOWS OF CHRONIC PULMONARY TUBERCULOSIS[1]

PHILIP H. PIERSON

Careful X-ray studies of pulmonary disease have been of great assistance in visualizing the type, location and extent of lesions, and for several years roentgenologists, pathologists and clinicians have endeavored to correlate their findings more accurately. Dunham, in 1915, presented a series of cases studied by careful physical examination and stereoscopic roentgenographs. The study of roentgen shadows in three dimensions gave information not obtained from the superimposed shadows in a flat plate. Recently, some roentgenologists have felt that a more accurate interpretation of the shadows is obtained by a study of the posteroanterior and lateral views than by the stereoscopic method. This procedure helps to visualize lesions back of the heart, and anterior and posterior to the dome of the diaphragm, and enables one to determine their depth and their relation to interlobar septa.

The correlation of the etiology, extent and location of disease, as seen postmortem and in the roentgenograph, has been brought out by the work of Ziegler and Krause, Schut and van Dehn, von Romberg, Assmann and others, but their work represented very gross comparisons. Later, Brauer and Beneke excised the lungs, filled them with formalin, and made serial sections. The disadvantage in this method of study was that excised lungs did not maintain the size and shape present when confined in the rib-cage. Hansen and von Loeschke overcame this obstacle by injecting eight to ten litres of a 10 per cent formalin solution into the saphenous vein, thereby hardening the lungs *in situ* within 12 to 24 hours. The ribs could then be removed without disturbing the shape of the lungs. Using this method, Gräff and Küpferle studied 52 thoraces sectioned in numerous frontal planes, and compared the disease present with the physical signs and the roentgenographs taken as shortly before death as possible. The course of the disease was also reported.

[1] From the Department of Medicine, Stanford University Medical School, San Francisco, California.

Their work, published in 1923, is most instructive in visualizing the extent of the disease.

The work here reported was started in 1923, and was undertaken to study and visualize the pulmonary disease causing the death of a tuberculosis patient. The patient's history and physical examination were as follows:

A. B., male, aged 64, ship-joiner, entered the Stanford Service, San Francisco Hospital, June 27, 1923.

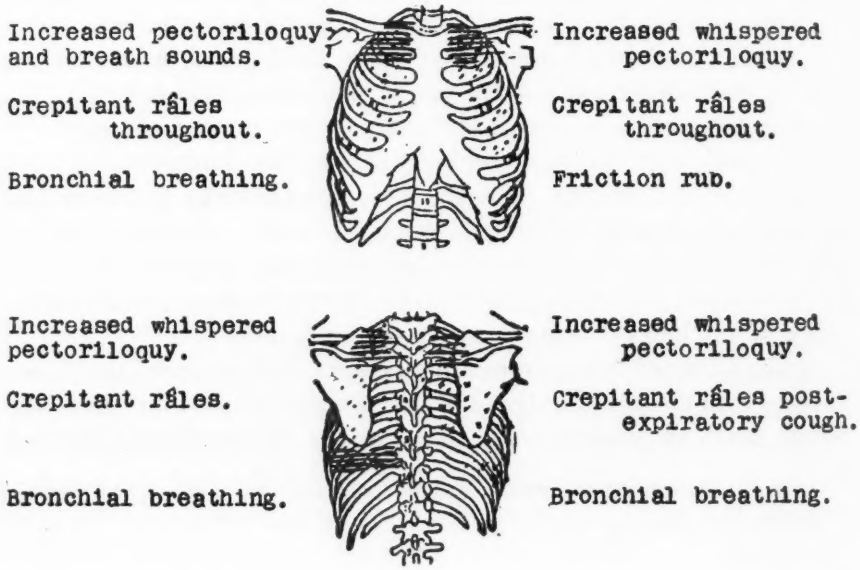
P. I.: He felt well until one and one-half years before admission, when he noticed a gradual loss of 40 pounds in weight, and the onset of a dry cough. In time this became productive, and he had a "choked-up" feeling in his chest, and the increasing dyspnoea and weakness caused him to stop work two weeks prior to his admission. He had frequent, but not burning, urination for the three months before entry. He complained of considerable gas in his stomach. There had been no pain in the chest, or night-sweats.

P. H.: There had been no respiratory illness prior to the present illness.

F. H.: There was no tuberculosis in his family, nor had there been any known exposure to it.

P. E.: *Chest:* poorly nourished, prominent supraclavicular and infraclavicular fossae. Limitation of motion of both chests; right moves more freely than left.

The auscultatory findings are shown on the accompanying diagrams.



Death occurred November 13, 1923.

The body was received 36 hours after death, and roentgenographs were taken in the posteroanterior projection at five feet.

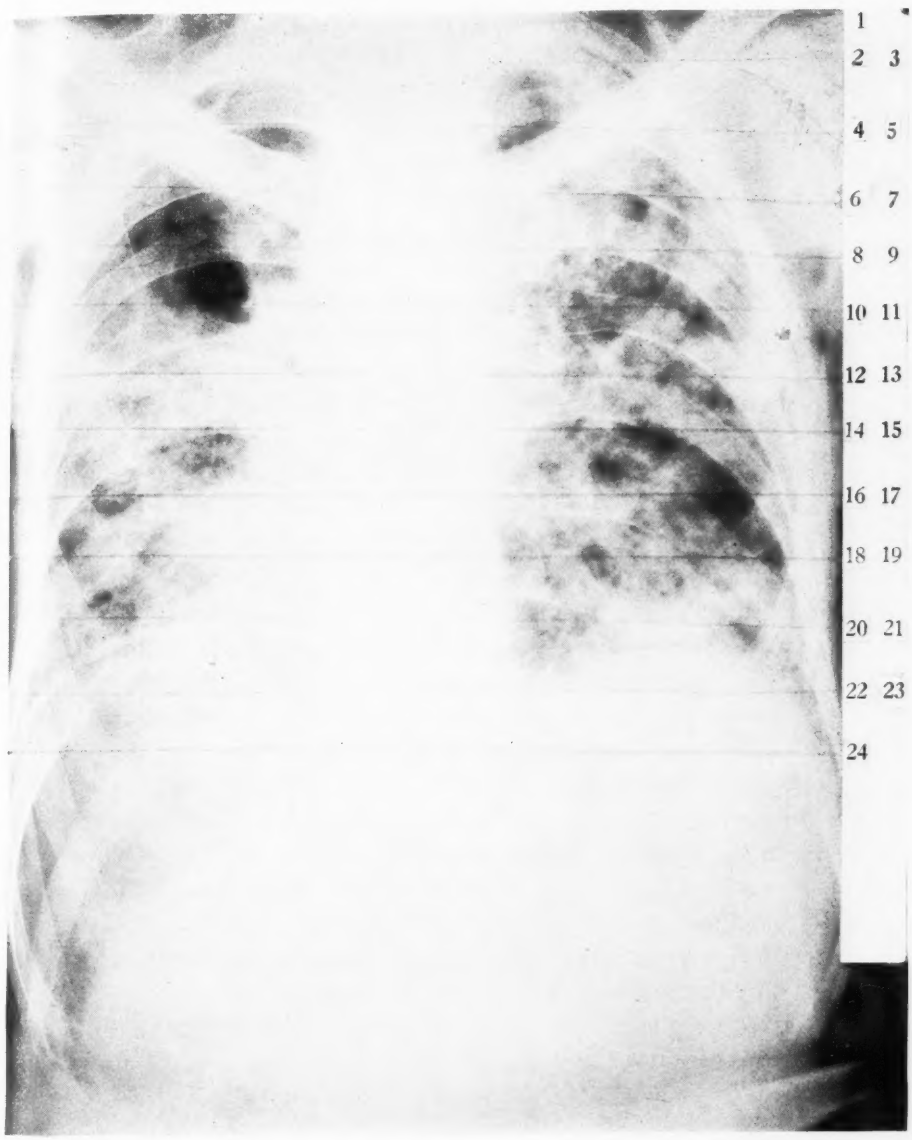


FIG. I. POSTERO-ANTERIOR ROENTGENOGRAPH TAKEN AT DISTANCE OF 5 FEET

Lines represent location of cuts through thorax, and figures refer to photographs of upper and lower aspects of sections.

The roentgenological report by Dr. R. R. Newell was as follows:

There is a large mass of air in the upper portion of the left chest. Some of this seems to burrow into the lung; but over a large part of the outer surface no lung tissue can be seen. There is what looks to be quite obviously a cavity in the right apex, and there are some suspicious annular shadows of small size in the lower lobes.
There is a great deal of fuzzy density scattered in a feathery sort of way through both lung fields. I suspect this is a postmortem change.

The body was embalmed, and the thorax severed and frozen. A mitre was constructed, which allowed us to cut sections on a five-foot radius, following the plane of the X-rays. The location of the cuts is shown by the horizontal lines in the roentgenograph, figure I. These sections measured approximately 1 to 2 cm. in thickness anteriorly, and slightly less posteriorly. A study of any one of the sections shows the disease represented by the superimposed shadows in the corresponding strip on the roentgenograph.

A model was prepared by tracing in different colors the important shadows on a glass plate for each of the sections (figure II). This can be viewed in a light box, either upward through the diaphragm or from the apices downward, and should be of value to the student in his correlation of physical signs and underlying disease.

The photographs taken by Dr. F. E. Blaisdell represent the upper and under surfaces of each section.

A pathological study of the sections showed a diffuse fibrocaseous process throughout both lungs, especially in both upper lobes, which had probably existed for a longer period than the patient related in his story. The disease in the lower lobes was more marked anteriorly than posteriorly, although there were areas of bronchopneumonia in the posterior lower portion. There was a large cavity in each apex, much larger in the left than in the right, and in both lungs were numerous smaller cavities, which are very graphically demonstrated below the dome of the diaphragm and behind the heart in figures 19 to 23. Apparently the spread of the disease was by the lymphatics and bronchial tubes, and not by the blood-stream.

It is apparent that the pneumothorax, which was suggested by the appearance of the roentgenograph, was, in reality, a large cavity in the left upper lobe.

Another point of interest was the emphysema present in the anterior chest. This emphysema was due to the contraction of fibrous tissue deposited about cavities, and throughout the parenchyma of the lung

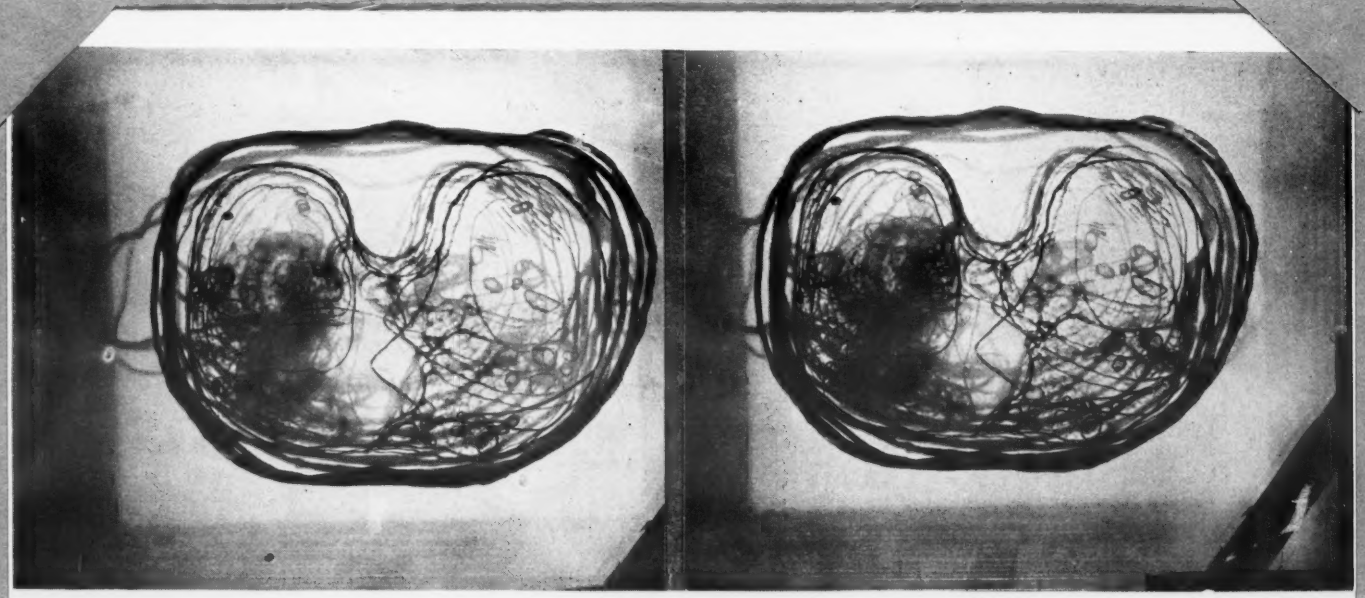


FIG. II. STEREOSCOPIC VIEW OF GLASS MODEL, VIEWED UPWARD THROUGH THE DIAPHRAGM

in the process of healing not associated with cavitation. "Compensatory emphysema," in this type of fibrosis, represents compensation in space and not in function.

CONCLUSION

Horizontal sectioning through the thorax offers a method of studying carefully all the disease in a given section of the roentgenograph, including that which is otherwise obscured by the heart and diaphragm, and correlating it with the physical signs. It also offers a means of visualizing parts (chambers, great vessels, etc.) of the heart in the roentgenograph. It is hoped that more work of this kind may be done, especially in cases in which less disease is present.

I am indebted to Drs. Blaisdell and Newell for their many suggestions and valuable assistance.

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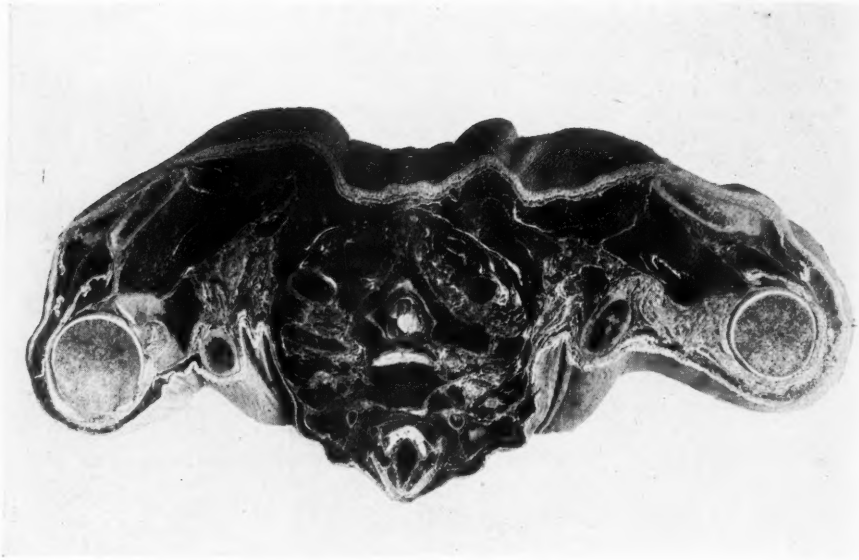
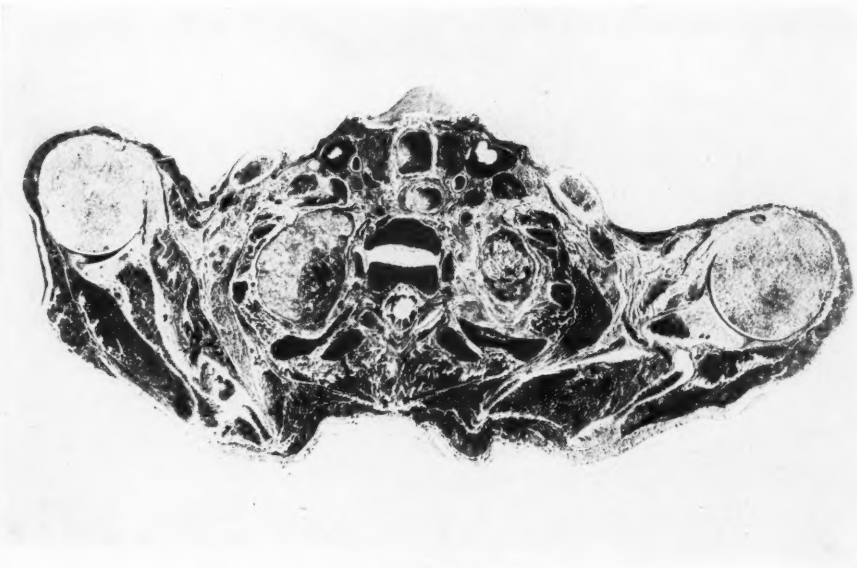




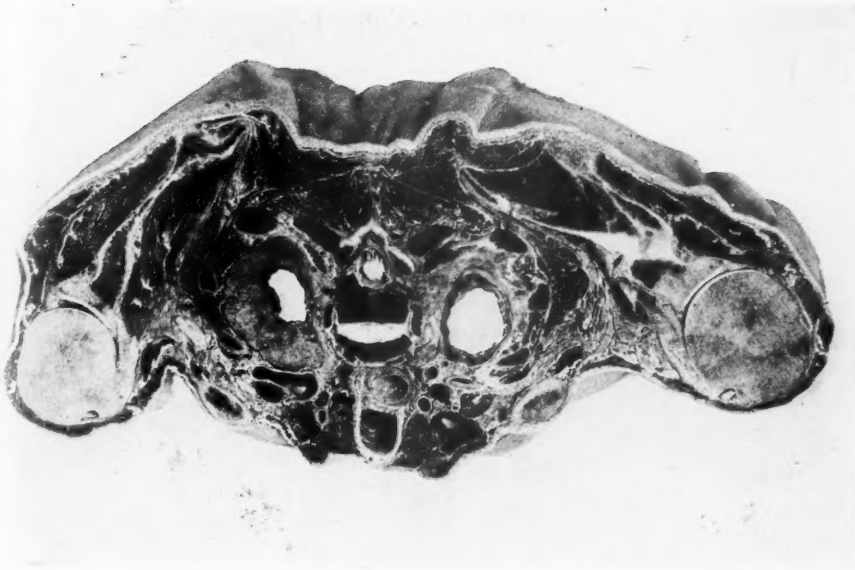
Section 1

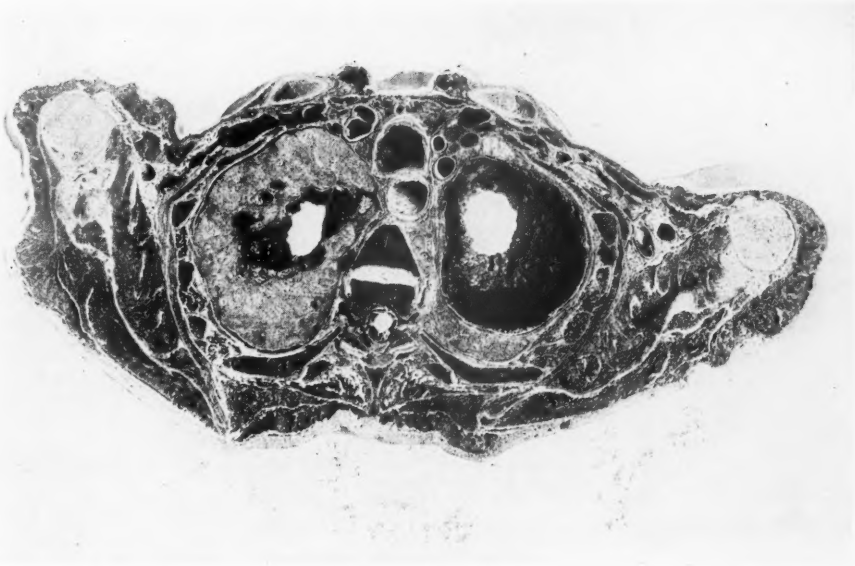
FIG. 1. UPPER SURFACE

Right Lung: The pleura of the apex is barely visible.

FIG. 2. LOWER SURFACE

Right Lung: Dome of cavity close to inner aspect.
Left Lung: Pleural thickening over apex.





Section 2

FIG. 3. UPPER SURFACE

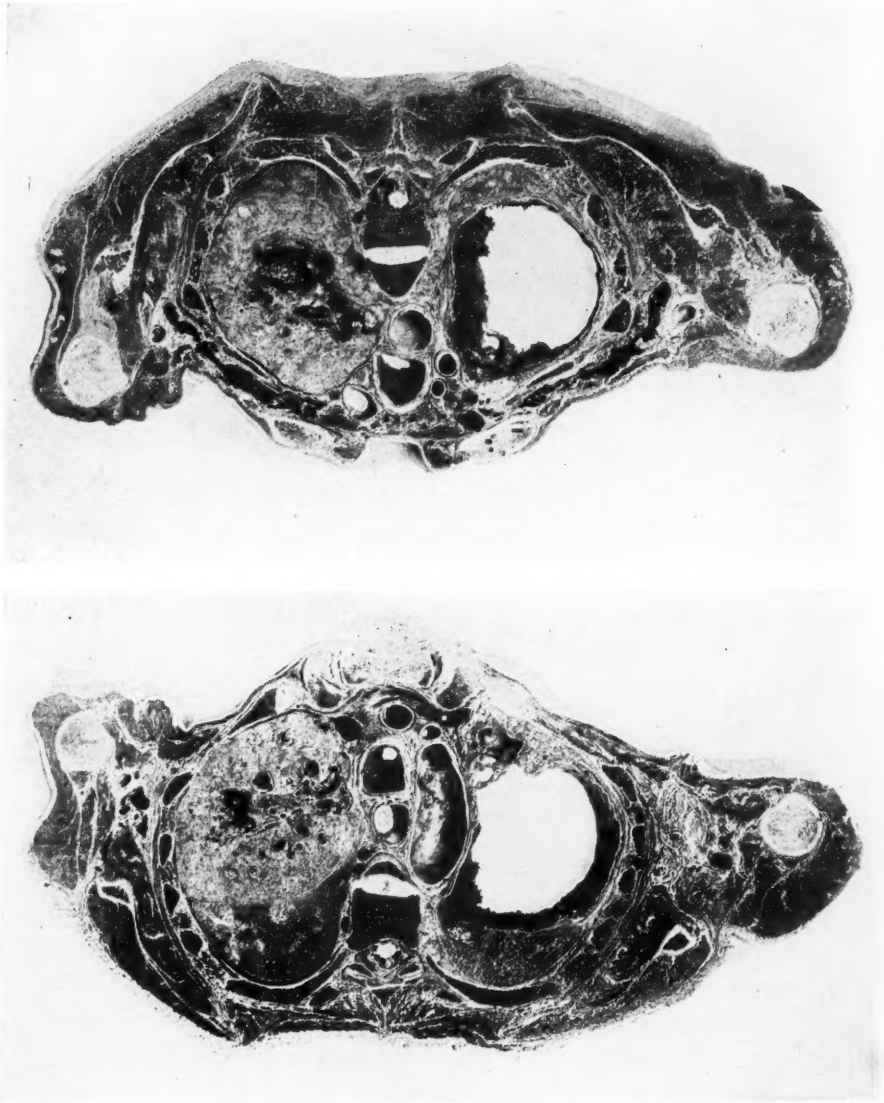
Right Lung: Cavity at the apex is more evident. Surrounded by fibrocaseous infiltration.

Left Lung: Cavity entirely replaces lung tissues.

FIG. 4. LOWER SURFACE

Right Lung: Cavity burrowing into lung tissue apparently multilocular, surrounded by fibrocaseous infiltration. Interlobar septa and tip of lower lobe evident posteriorly.

Left Lung: Huge cavity occupying most of this section with small amount of fairly normal lung posteriorly.



Section 3

FIG. 5. UPPER SURFACE

Right Lung: Lower part of multilocular cavity surrounded by fibrocaseous infiltration. Lower lobe evident posteriorly.

Left Lung: Cavity entirely replacing lung except for small area anteriorly and posteriorly.

FIG. 6. LOWER SURFACE

Right Lung: Extensive multilocular cavitation in close proximity to larger bronchi. Emphysema present anteriorly, due to fibrosis. Lower lobe shows few areas of caseous pneumonia.

Left Lung: Large cavity still present very close to arch of the aorta.

Section 4

FIG. 7. UPPER SURFACE

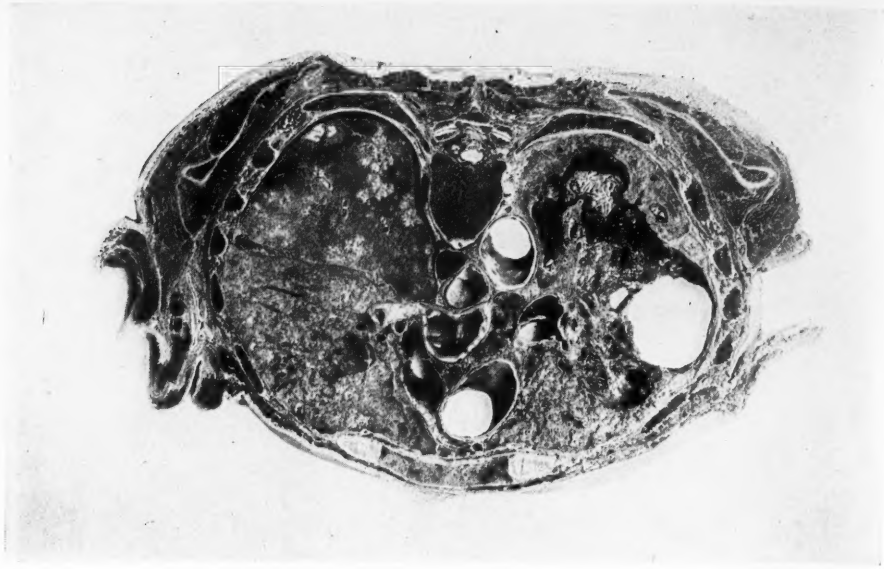
Right Lung: Fibrosis surrounding multilocular cavities. Few areas of caseous pneumonia in right lower lobe.

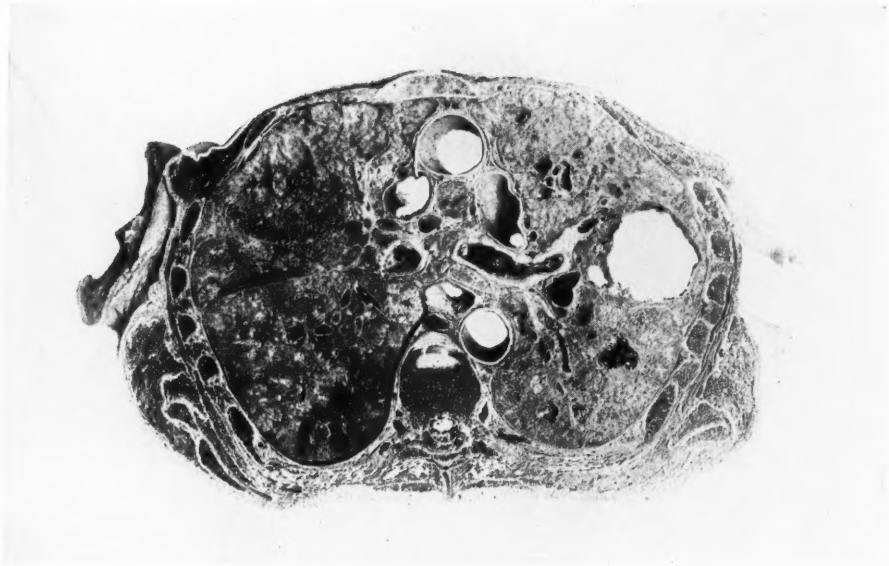
Left Lung: Inner wall of cavity with several fibrous blood-vessels, especially in posterior part.

FIG. 8. LOWER SURFACE

Right Lung: Upper lobe shows marked emphysema caused by fibrosis. Lower lobe shows scattered caseous pneumonia.

Left Lung: Extension of cavity through to posterior aspect of lung. Anterior to this is fibrosis with emphysema.





Section 5

FIG. 9. UPPER SURFACE

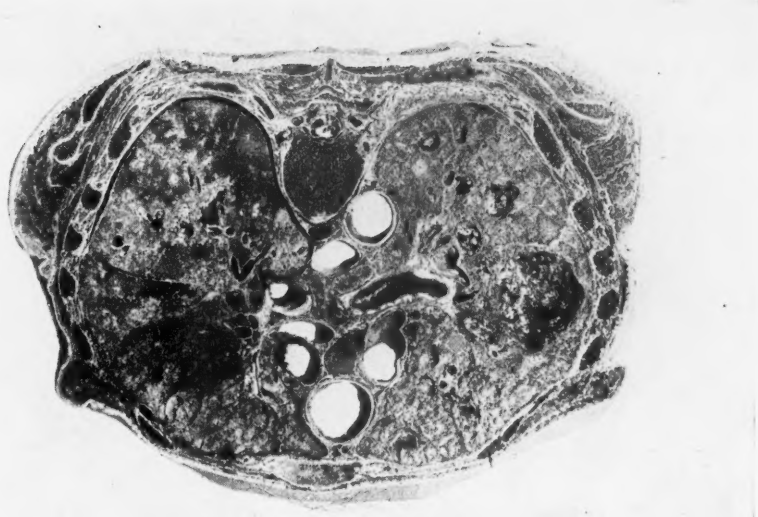
Right Lung: The upper lobe shows emphysema. At the outer end of the interlobar septum the tip of the middle lobe is evident. It is interesting to note the size attained by the lower lobe at the point where the middle lobe begins. The lower lobe is normal except for areas of caseous pneumonia.

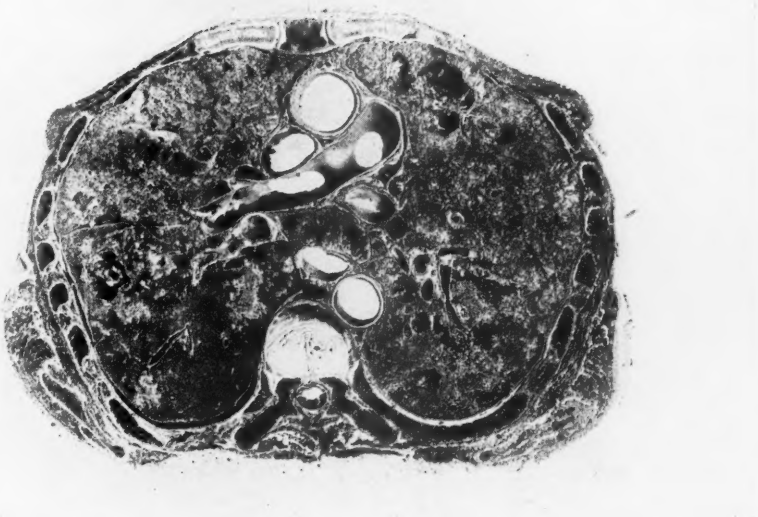
Left Lung: Emphysema anteriorly. The shelving wall of the cavity is markedly fibrotic.

FIG. 10. LOWER SURFACE

Right Lung: Upper lobe shows fibrosis with emphysema. The middle lobe shows areas of caseous pneumonia. The lower lobe shows few cavities centrally located, with areas of caseous pneumonia scattered throughout anterior two-thirds.

Left Lung: The upper lobe shows fibrosis and emphysema and the communication of the cavity with a bronchus. Interlobar septum evident, and a fibrocaseous infiltration in the lower lobe with small cavities.





Section 6

FIG. 11. UPPER SURFACE

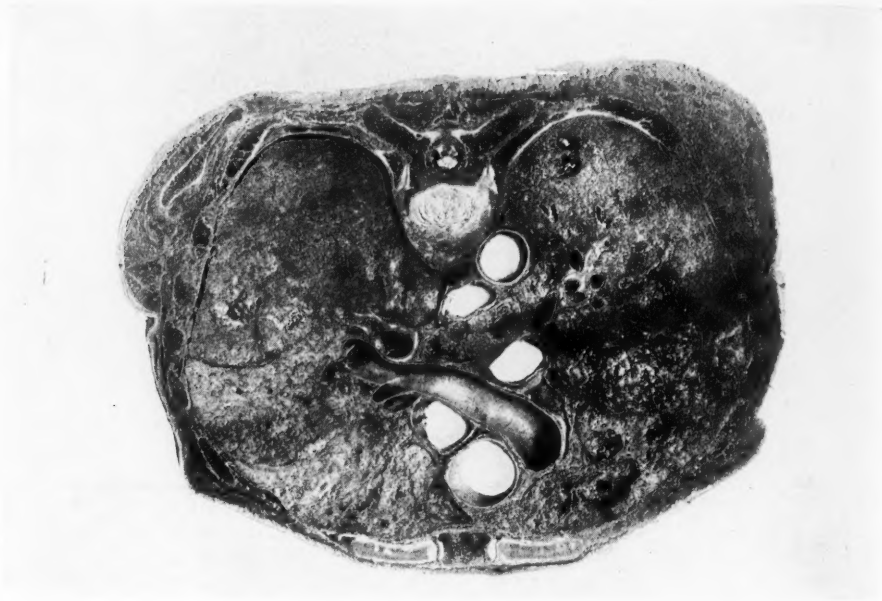
Right Lung: The upper lobe shows fibrosis with emphysema. The middle lobe shows a few areas of caseous pneumonia definitely encircling bronchi.

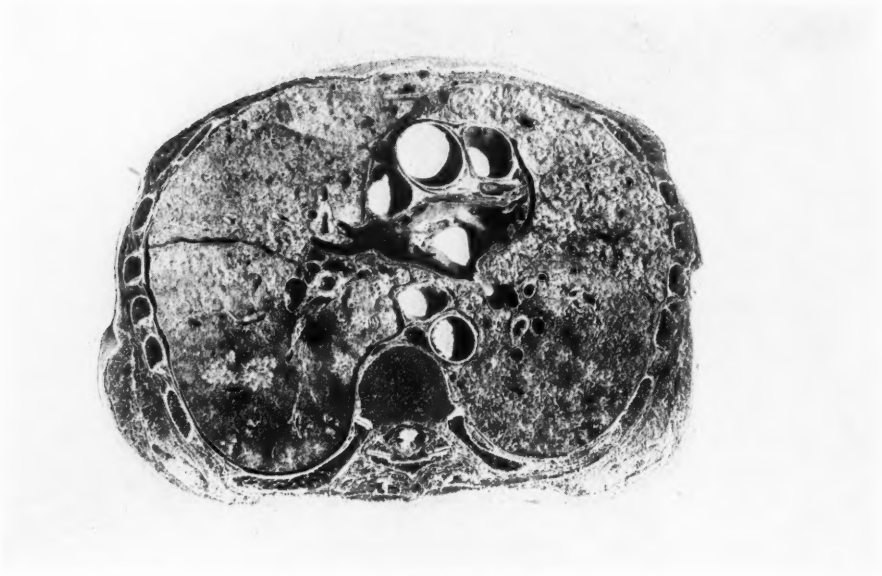
Left Lung: The upper lobe shows emphysema and cavitation. The lower lobe shows fibrocaseous infiltration with several cavities.

FIG. 12. LOWER SURFACE

Right Lung: The upper lobe shows fibrosis with emphysema. The middle lobe shows fibrocaseous infiltration. The lower lobe shows caseous pneumonia with cavitation in the anterior portion. A small pneumonic area is seen distal to a branching bronchus.

Left Lung: The upper lobe shows emphysema with several cavities, one of which is anterior to the pulmonary artery and therefore not visible in roentgenograph. The lower lobe shows fibrocaseous infiltration throughout. The large blood-vessel passing from left to right is the pulmonary artery.





Section 7

FIG. 13. UPPER SURFACE

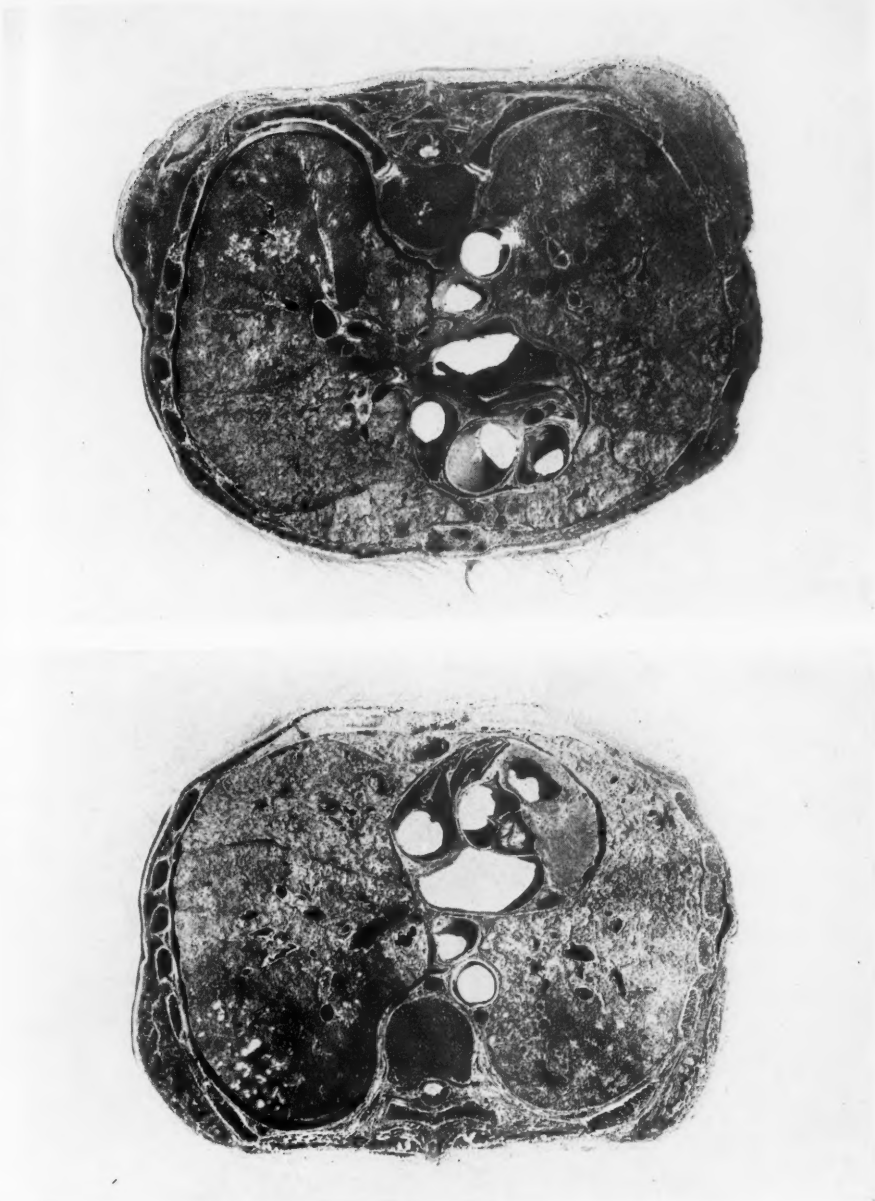
Lower half of pulmonary artery is seen crossing from left to right.

Right Lung: Upper and middle lobes show emphysema and diffuse fibrosis. Lower lobe is normal except for a few small areas of caseous pneumonia.

FIG. 14. LOWER SURFACE

Right Lung: Shows fibrosis with emphysema, and several small cavities anterior to heart shadow and not seen in the rentgenograph. The middle lobe shows fibrosis with emphysema. The lower lobe shows a few patches of caseous pneumonia.

Left Lung: Shows fibrocasecus infiltration with emphysema anteriorly.



Section 8

FIG. 15. UPPER SURFACE

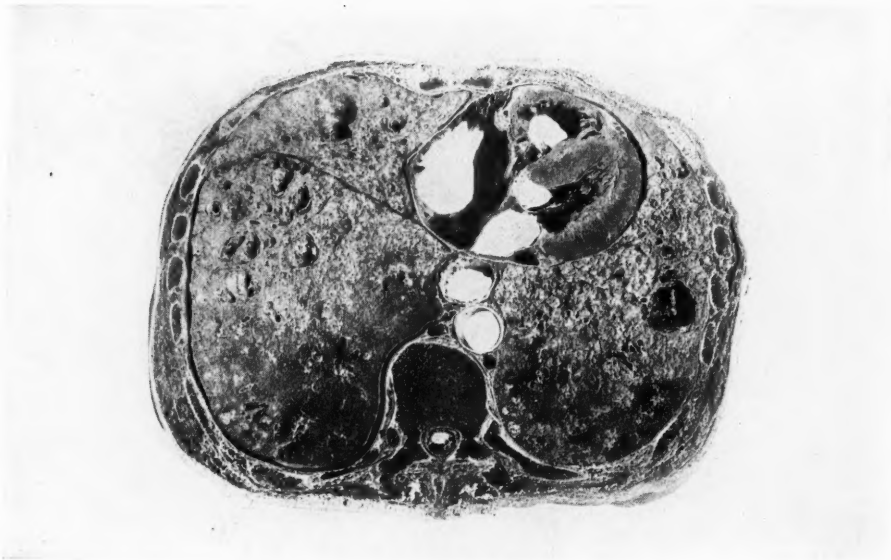
Right Lung: Upper and middle lobes show fibrosis with emphysema. Lower lobe shows few small areas of caseous pneumonia about bronchi.

Left Lung: Shows fibrosis with emphysema anteriorly and fairly normal lung posteriorly.

FIG. 16. LOWER SURFACE

Right Lung: A cavity is seen in the tip of the upper lobe, anterior to the heart shadow, and not visible in the roentgenograph. The middle lobe shows fibrosis with emphysema. The lower lobe shows fibrosis with emphysema anteriorly, and several areas of caseous pneumonia posteriorly.

Left Lung: Shows fibrocaseous infiltration with emphysema particularly marked about cavities.



Section 9

FIG. 17. UPPER SURFACE

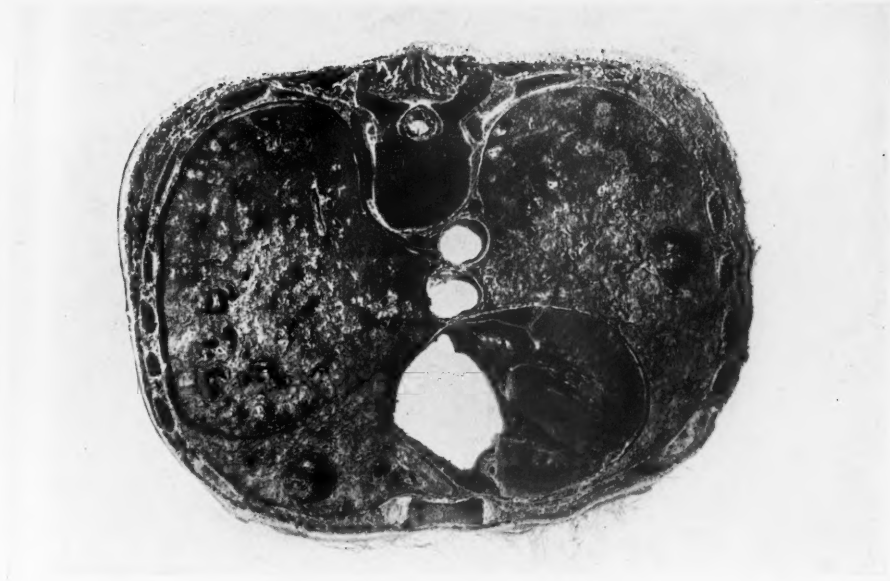
Right Lung: Tip of the upper lobe is just visible. The middle lobe shows fibrosis with several small cavities and marked emphysema. The lower lobe shows fibrosis with emphysema anteriorly, and small areas of caseous pneumonia posteriorly.

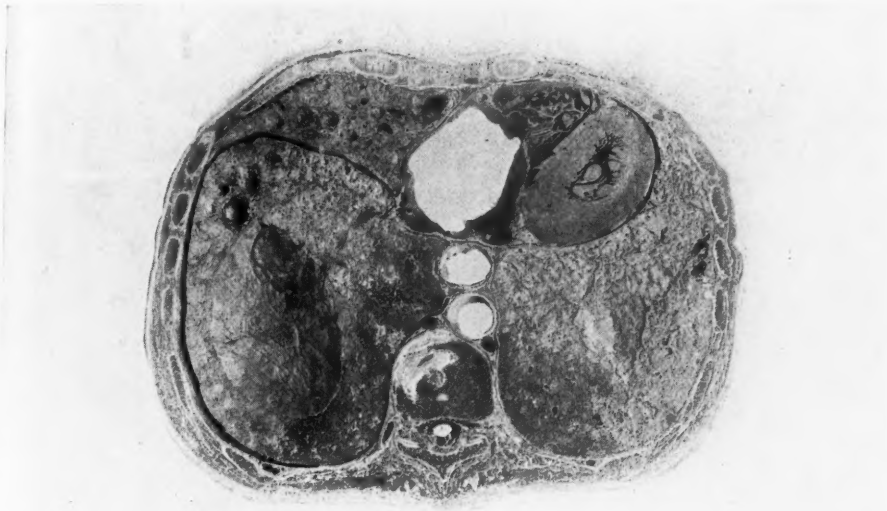
Left Lung: Shows fibrosis with emphysema in the anterior two-thirds, and small areas of caseous pneumonia posteriorly.

FIG. 18. LOWER SURFACE

Right Lung: The middle lobe shows fibrosis with cavitation and emphysema. The lower lobe, in the anterior half, shows fibrosis with cavitation and emphysema. The posterior half shows a few small areas of caseous pneumonia. It is interesting to note that the heart shadow at this level is composed of the left ventricle and the right auricle.

Left Lung: Fibrosis occupies the anterior two-thirds, with a large cavity near the periphery, while posteriorly there is a diffuse emphysema with a few small areas of caseous pneumonia.





Section 10

FIG. 19. UPPER SURFACE

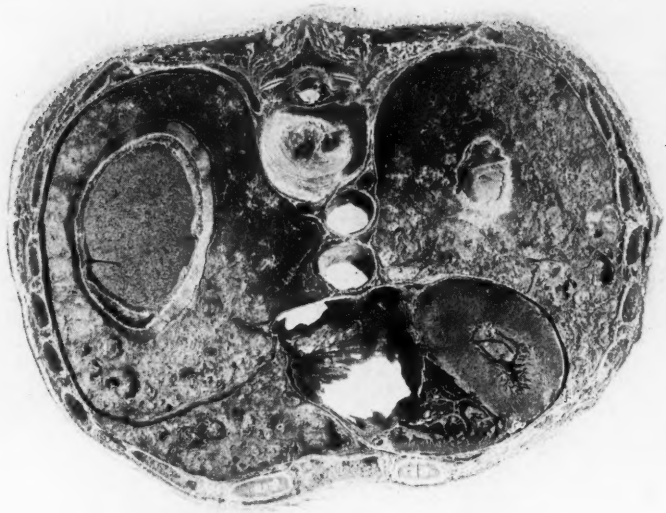
Right Lung: The middle lobe shows fibrosis with cavitation and emphysema. The lower lobe, in the anterior half, shows marked fibrosis and cavitation with emphysema. The posterior half shows a few small areas of caseous pneumonia.

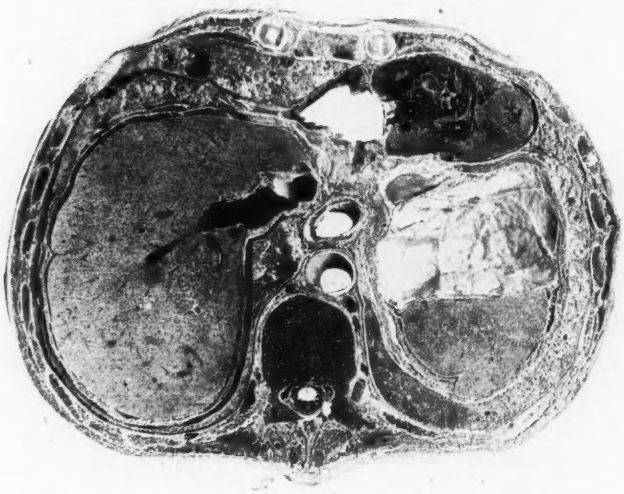
Left Lung: The anterior two-thirds shows fibrosis with a large cavity and diffuse emphysema, while posteriorly a few small areas of caseous pneumonia exist.

FIG. 20. LOWER SURFACE

Right Lung: The middle lobe shows fibrosis with several cavities, one anterior to the right auricle and obscured by it in the roentgenograph. The lower lobe shows imprint of the dome of the diaphragm. Anterior to this several cavities are evident, obscured by the dome of the diaphragm in the roentgenograph.

Left Lung: The anterior two-thirds shows fibrosis with emphysema.





Section 11

FIG. 21. UPPER SURFACE

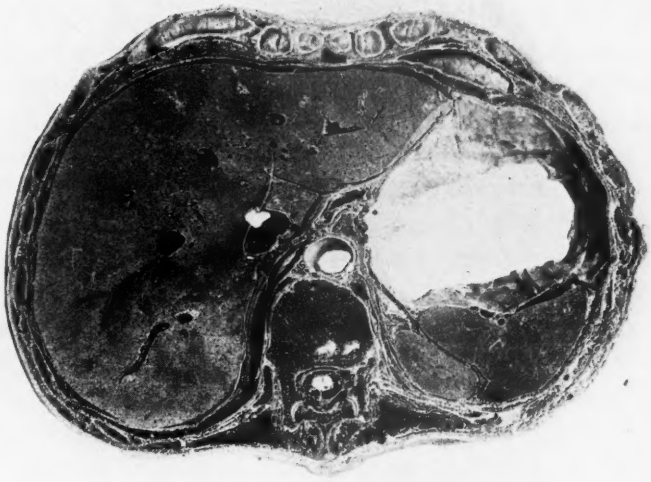
Right Lung: The middle and lower lobes, anterior to the cut surface of the diaphragm and liver, show fibrosis, cavitation and emphysema. Posteriorly, there are areas of caseous pneumonia.

Left Lung: Shows fibrosis with emphysema, except for a small area in the posterior inner portion which is fairly normal. The dome of the left lobe of the liver is seen in the middle of this field.

FIG. 22. LOWER SURFACE

Right Lung: Small tips of the middle and lower lobes are evident anteriorly, with a cavity in the middle lobe. Note the small amount of pulmonary tissue between the liver and the descending aorta.

Left Lung: A small rim of lung tissue exists about the liver.



Section 12

FIG. 23. UPPER SURFACE

Right Lung: A small amount of the middle and lower lobes is seen anteriorly, and is markedly fibrotic and contains cavities. At this level, too, a small portion of pulmonary tissue exists between the liver and great vessels.

Left Lung: There is a small fringe of lung tissue outside of the liver, and it shows fibrosis with emphysema.

FIG. 24. THE APEX OF THE HEART IS JUST VISIBEE AT THIS LEVEL

ARTIFICIAL PNEUMOTHORAX AT THE LOOMIS SANATORIUM OVER FOURTEEN YEARS[1]

A Clinical and Statistical Study[2]

ANDREW PETERS[3]

In recent years an increasing number of reports on a considerable series of cases of pulmonary tuberculosis treated by artificial pneumothorax has become available as the method has been practised more and more widely, sanatorium facilities have improved, and experience has accumulated. A few years ago comparatively few reports dealt with as many as 100 cases. We now have reports covering from several hundred to 1,000 or more (the Matsons (1) in this country, Burrell and MacNalty (2) in England, and Rist (3) in France, for example). Also, these recent reports are much more carefully analyzed and more nearly complete than most earlier ones, although the writings of Forlanini, Brauer and Spengler, Dumarest, Lillingston, Saugman, Floyd and Robinson, and other pioneers, are always worth going back to, and a careful perusal of them will note reference to most of the clinical features now provoking discussion.

The Loomis Sanatorium series is a rather composite one, including patients in whom treatment was begun or attempted between the years 1911 and 1923 inclusive, and followed up to July, 1925. The treatment was under the direction of several different men, beginning with King and Mills, and since 1918 it has been carried on by myself and coworkers under the late Doctor Bertram H. Waters as Physician-in-Chief. During the first part of this period very few patients were given pneumothorax treatment (75 in the years 1911–1917), but since 1917 about three times as many patients per year, on the average, have had pneumothorax induced or attempted (see table 1), the maximum of 41 being reached during the years 1919–1920, the year following the influenza

[1] Read in abstract at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 26, 1927.

[2] From the Loomis Sanatorium, Loomis, N. Y.

[3] Pittsfield, Massachusetts.

pandemic, when it seemed to us, as noted by Tewksbury (4) and others, that an especially large number of suitable, often practically unilateral, cases of tuberculosis, often of quite brief duration, was admitted. (We refer to actually manifest tuberculosis, proved by the finding of tubercle bacilli in the sputum.)

We have not in this paper attempted to separate the earlier from the later series in the study, although it seems obvious from our records that the former contained a much poorer lot of material, and a larger proportion of unsuccessful cases (operative failures, etc.) and that in many the treatment was not continued long enough to expect any noteworthy results.

The proportion of patients admitted in whom pneumothorax has been induced or attempted has remained at from 12 to 15 per cent of definitely diagnosed cases of pulmonary tuberculosis in recent years, and of patients now residing in the Sanatorium about 20 per cent have had pneumothorax given or attempted.

This series includes 273 patients, or 275 cases, the discrepancy being due to the fact that two of the patients were treated over two distinct and separate periods, having their lungs recollapsed because of symptoms of reactivation after they had been allowed to expand. Nine patients are omitted from consideration who received what was designated "incidental pneumothorax," that is, to replace exudate in 5 cases, and to continue for a brief time an accidental spontaneous pneumothorax, 4 cases. Three definitely nontuberculous cases treated by pneumothorax are also omitted, and two with tuberculosis questionable (one probably a neoplasm).

TABLE 1

YEAR BEGUN	CASES TREATED	YEAR BEGUN	CASES TREATED
1911	6	1918	38
1912	10	1919	41
1913	15	1920	41
1914	11	1921	30
1915	9	1922	18
1916	11	1923	32
1917	13		
1911 to 1917	75	1918 to 1923	200

TABLE 2

Classification of cases according to stage of disease

	FAR ADVANCED	MODERATELY ADVANCED (P) FAR ADVANCED (R)	MODERATELY ADVANCED	INCIPIENT (P) MODERATELY ADVANCED OR FAR ADVANCED (R)
	per cent	*per cent*	*per cent*	*per cent*
Cases with satisfactory collapse....	46 (49.5)	23 (24.7)	22 (23.7)	2 (2.1)
Incompletely effective collapse.....	71 (66.4)	30 (28.0)	5 (4.7)	1 (0.9)
Temporary or undetermined collapse.....	17 (94.4)	0	1 (5.6)	0
All above combined.....	134 (61.5)	53 (24.3)	28 (12.8)	3 (1.4)
Pneumothorax impossible (operative failures).....	44 (77.2)	7 (12.3)	6 (10.5)	0
All cases combined.....	178 (64.4)	60 (21.8)	34 (12.4)	3 (1.1)

Our material is made up largely of patients whose disease was classified as in the far-advanced stage, on clinical grounds alone in nearly two-thirds, in over 85 per cent with the aid of roentgenographs. (As this was before the revision of the classification a still larger proportion would at present be considered far advanced.) Table 2 shows the proportion of patients in each stage of the disease, for the group as a whole, and for various subgroups. It will be noted that the "operative failure" and "undetermined collapse" groups contain the largest proportion of subjects in the far-advanced stage, but, if X-ray revision of classification be considered, the "incompletely effective" group shows almost as many.

In going over the records we have noted particularly those patients in whom pneumothorax treatment seemed only a *desperate last resort.* There were 88 of such cases in all, 32 per cent, or approximately one-third. Probably closer scrutiny would cause more to be placed in this category. They are distributed as shown in table 3 among the various groups that we shall discuss later.

TABLE 3

Among total operative failures (no pneumothorax possible).....	51 per cent were desperate last resort
Among incompletely effective collapse cases.....	36 per cent were desperate last resort
Among satisfactory or effective collapse cases.....	12 per cent were desperate last resort
Among group of temporary or undetermined collapse cases.....	70 per cent were desperate last resort

The type of operative results secured confirms the pretty generally held opinion that the chances of success in cases of last-resort are almost infinitesimal; it is obvious, therefore, that the man who hesitates and delays so long before instituting pneumothorax that his patients selected are far on the down grade, with very advanced lesions, or who uses the method too indiscriminately in well-marked cases of bilateral disease, is going to have almost uniformly poor success, and either become prejudiced against using pneumothorax at all or, what is more likely, his patients will refuse to have it, having heard that nearly all who took the treatment failed to live long afterward and were no better off for it.

The previous course of the disease was undoubtedly active and progressive in 243 of the 275 cases (88 per cent), while activity was slight or questionable in the remaining 32 (12 per cent). A considerable portion of the latter had been collapsed to control haemoptysis, which is almost presumptive evidence of activity, while others were more or less chronic fibroid cases, probably more or less active. (Tables 4, 5 and 6.)

TABLE 4

General condition prior to treatment

	per cent
Good or fair	44.9
Impaired	33.7
Much impaired	21.4
	100.0

TABLE 5

Degree of collapse obtained

		per cent
Satisfactory or effective	93	(33.8)
Incomplete or partly effective	107	(38.9)
Undetermined or temporary	18	(6.5)
None (operative failure)	57	(20.8)
	275	(100.0)

TABLE 6

Clinical type of disease

		per cent
Acute phthisis	27	(9.8)
Subacute, subchronic or intermediate	162	(58.9)
Very chronic	86	(31.3)
	275	(100.0)

The division of the clinical types of the disease into roughly (1) acute, (2) subacute, subchronic or intermediate, and (3) chronic, is necessarily somewhat arbitrary, as the dividing lines are not clear-cut. A previously chronic case may suddenly undergo an acute progression, while a history of short duration may be misleading, and closer study convince us that the disease has pursued an insidious, chronic course. Hence, we could not rely entirely upon the presumable duration of the disease as gathered from the clinical history, although this was very

TABLE 7

Distribution of clinical types among collapse groups

CLINICAL TYPE	SATISFACTORY COLLAPSE	INCOMPLETELY EFFECTIVE COLLAPSE	OPERATIVE FAILURE
	per cent	*per cent*	*per cent*
Acute	10.6	7.7	7.0
Subacute, subchronic or intermediate	73.4	56.8	35.1
Very chronic	16.0	35.5	57.9
	100.0	100.0	100.0

TABLE 8

Presumable duration of disease prior to beginning pneumothorax

	SATISFACTORY COLLAPSE GROUP: 93 (92)		INCOMPLETELY EFFECTIVE COLLAPSE: 107 (106)		COLLAPSE TEMPORARY OR UNDETERMINED: 18		OPERATIVE FAILURES: 57	
		per cent		*per cent*		*per cent*		*per cent*
Not exceeding 6 months	25	(26.9)	12	(11.2)	3	(16.7)	5	(8.8)
7 to 12 months	19	(20.4)	20	(18.7)	6	(33.3)	6	(10.5)
13 to 24 months	15	(16.1)	30	(28.0)	4	(22.2)	16	(28.1)
More than 24 months	30	(32.3)	43	(40.2)	5	(27.8)	28	(49.1)
Uncertain	4	(4.3)	2	(1.9)			2	(3.4)
	93	(100.0)	107	(100.0)	18	(100.0)	57	(99.9)

helpful; clinical observation and judgment, therefore, were also used in placing each case in one of these three groups.

From table 7 it is seen that acute phthisis is about evenly represented in each group, making up somewhat over 10 per cent of the "satisfactory collapse" group and 7 to 8 per cent of the other groups. The very chronic cases increase from 16 per cent in the "satisfactory collapse" group to 35 per cent in the "partly effective" group and reach 58 per cent among the "operative failures."

This is good evidence that the more chronic the type of case the less likely is a satisfactory collapse to be obtained and the more likely is the case to be an operative failure. However, it also appears that many of

TABLE 9

Duration of pneumothorax treatment (at the Sanatorium)

	SATISFACTORY COLLAPSE GROUP: AVERAGE 15.8 MONTHS +		INCOMPETELY EFFECTIVE COLLAPSE: AVERAGE 9.2 MONTHS		COLLAPSE TEMPORARY OR UNDETERMINED: AVERAGE 3.8 MONTHS	
		per cent		*per cent*		*per cent*
Not exceeding 6 months	9	(9.7)	51	(47.7)	14	(77.8)
7 to 12 months	22	(23.7)	25	(23.3)	2	(11.1)
13 to 24 months	50	(53.8)	24	(22.5)	2	(11.1)
25 to 36 months	11	(11.8)	7	(6.5)		
37 to 48 months	1	(1.1)				
	93	(100.1)	107	(100.0)	18	(100.0)

TABLE 10

*Complications existing prior to pneumothorax treatment**

	SATISFACTORY COLLAPSE GROUP		INCOMPLETELY EFFECTIVE COLLAPSE		COLLAPSE TEMPORARY OR UNDETERMINED		OPERATIVE FAILURES
		per cent		*per cent*		*per cent*	
Tuberculous enteritis	9	(9.9)	13	(12.2)	4	(22.2)	Data incomplete
Tuberculous laryngitis	6	(6.5)	9	(8.4)	3	(16.7)	
Tuberculous peritonitis	1	(1.1)	1	(0.9)			
Tuberculous otitis			1	(0.9)			
Tuberculous lymphadenitis					1	(5.6)	
Ischiorectal abscess	1	(1.1)					
Diabetes mellitus			2	(1.9)			
Syphilis			2	(1.9)			
Chronic endocarditis			1	(0.9)			
Marked secondary anaemia	1	(1.1)	1	(0.9)			

* This list of complications is almost certainly incomplete, as some of the records, especially of patients under observation but a short time, are rather meagre. The diagnosis of tuberculous enteritis was in a great many cases based only on symptoms, but is probably not overestimated, while the number of laryngitis cases is probably actually greater than recorded, many patients being so ill that complete examination was not deemed advisable. The course followed by these tuberculous complications was often strikingly parallel to that of the pulmonary condition. Exacerbations of enteritis symptoms were often noted during the early part of treatment, before convalescence was under way and accompanying febrile reactions or severe pleurisies.

the acute forms are also associated with adhesions and are unsuccessful for these reasons, as will be further shown later on.

This "presumable duration of disease" (see table 8) was based on the history records, and represents the historian's opinion. It is interesting to note that the "satisfactory collapse" group contains the largest proportion of cases with symptoms of shorter duration, and the fewest of very long duration, while the reverse is true in the "operative failure" group, the "partly or incompletely effective collapse" group coming in between. Thus, as would be expected, the chances of obtaining a satisfactory or effective collapse diminish with the previous duration of the disease. Nevertheless, exceptions are quite common, pleural adhesions occurring early in some cases, and in others failing to occur to any great extent, despite extensive pulmonary damage.

Table 9 shows that most of the "satisfactory collapse" group received between one and two years' pneumothorax treatment at the sanatorium (and a considerable number continued it after leaving), while only about half of the "incompletely effective" group were treated over six months and only about one-quarter for over a year. Of the "temporary or undetermined collapse" groups, over three-fourths were terminated under six months, the average period being less than four months.

COMPLICATIONS ENCOUNTERED DURING COURSE OF PNEUMOTHORAX TREATMENT OR SUBSEQUENTLY NOTED

Tables 11, 12 and 13 reveal some interesting facts about the complications occurring in this series of pneumothorax cases, especially as to the pleuritic complications. First, the acute forms of the disease were most often associated with pleurisies (62.5 per cent) and most often with severe pleurisies (over 50 per cent), while the very chronic forms showed the lowest incidence and least severity of pleurisies. The "desperate last resort" cases showed a very high incidence except in those under observation for very brief periods and the great majority of these pleurisies were severe. Purulent and septic exudates were common. All but one of the septic-exudate cases also showed tubercle bacilli, but a few were not frankly purulent and did not become so. The most severe, a pure pneumococcus infection, caused death within a few days without demonstrable perforation of the lung. Purulent exudates were twice as frequent when collapse was incompletely effective as when it was satisfactory, and demonstrable bronchopleural fistula occurred six times as frequently. This suggests the rôle played by ruptured adhesions and superficial caseous or cavitated areas. Such demonstrable rupture or

perforation occurred in over 10 per cent of "desperate last resort" cases despite their very short average period of treatment. Pyogenic or septic infection of the pleura, while uncommon, occurs sufficiently often to make careful bacteriological examination advisable in the case of all exudates that cause serious symptoms. In our use of the term, *Severe Forms of Pleurisy*, we mean those causing more than transitory local,

TABLE 11

Complications occurring in different degrees of collapse grouping

	SATISFACTORY COLLAPSE (93)	INCOMPLETELY EFFECTIVE (107)	TEMPORARY OR UNDETERMINED (18)	COMBINED SUMMARY (218)
Pleurisy, exudative	53 (57.0%)	51 (47.7%)	6 (33.3%)	110
Severe forms	29 (31.2%, or 54.7% of exudative)	35 (32.7%, or 68.6% of exudative)	4 (22.2%, or 66.7% of exudative)	68
Purulent forms	7 (7.5%, or 13.2% of exudative)	16 (15.0%, or 31.4% of exudative)	2 (10.7%, or 33.3% of exudative)	25
Septic forms	4 (4.3%, or 7.5% of exudative)	5 (4.7%, or 9.% of exudative)	?	9
Demonstrable broncho-pleural fistula	1 (1.1%, or 1.9% of exudative)	7 (6.5%, or 13.5% of exudative)	2 (?) (10.7%, or 33.3% of exudative)	8 (?) or 10 (?)
Tuberculoma or sinus of chest-wall	3 (3.2%, or 5.7% of exudative)	7 (6.5%, or 13.5% of exudative)	?	10
Pleurisy, contralateral, exudative	1 (1.1%)	2 (1.9%)	0	3
Extrapulmonary or generalized tuberculosis	8 (8.6%)	6 (5.6%)	?	14
Meningitis	4 (4.3%)	1 (0.9%)		5
Enteritis	3 (3.2%)	5 (4.7%)	?	8
Ischiorectal abscess	1 (1.1%)			1
Accidents or untoward reactions		2 (1.9%)		2
Chronic nephritis, amyloid (?)		2 (1.9%)		2

constitutional or functional disturbance. The fact that exudates occurred even more frequently in the "satisfactory collapse" cases than in the others seems to indicate that the rupture of adhesions is not so important an etiological factor as has often been thought. Moreover, in some instances an exudate appeared during the process of reëxpansion of a collapsed lung after the cessation of refills. In this study we have

not taken up the end-results in all exudate cases. Some time ago Woolley and I (5) showed that as a group the end-results in a series studied differed very little from those in which no exudate was noted. However, it cannot be denied that a minority, associated with serious and irreparable pathological conditions, carry a grave or fatal prognosis.

TABLE 12

Complications occurring in different clinical types of disease treated

	ACUTE PHTHISIS (23)	SUBACUTE, SUBCRONIC OR INTERMEDIATE FORMS (142)	VERY CHRONIC FORMS (53)	COMBINED SUMMARY (218)
Pleurisy, exudative	15 (65.2%)	72 (50.7%)	23 (43.4%)	110 (50.5%)
Severe forms	12 (52.2% or 75% of exudative)	45 (31.7% or 62.5% of exudative)	11 (26.8% or 47.8% of exudative)	68 (31.2% or 61.8% of exudative)
Purulent forms	4 (17.4% or 26.7% of exudative)	18 (12.7% or 25% of exudative)	3 (5.7% or 13% of exudative)	25 (11.5% or 22.7% of exudative)
Septic forms	1 (4.3% or 6.7% of exudative)	8 (5.6% or 11.1% of exudative)	0	9 (4.1% or 8.2% of exudative)
Demonstrable bronchopleural fistula	2 (8.7% or 13.3% of exudative)	8 (5.6% or 11.1% of exudative)	0	10* (4.6% or 9.9% of exudative)
Tuberculoma or sinus of chest-wall	1 (4.3% or 6.7% of exudative)	6 (4.2% or 8.3% of exudative)	3 (5.7% or 13% of exudative)	10 (4.6% or 9.9% of exudative)
Pleurisy, contralateral, exudative	1 (4.3%)	2 (1.4%)	0	3 (1.4%)
Extrapulmonary or generalized tuberculosis	3 (13.0%)	8 (5.6%)	3 (5.7%)	14 (6.4%)
Meningitis	1 (4.3%)	3 (2.1%)	1 (1.9%)	5 (2.3%)
Enteritis, peritonitis	2 (8.7%)	4 (2.8%)	2 (3.8%)	8 (3.7%)
Ischiorectal abscess		1 (0.7%)		1 (0.5%)
Chronic nephritis, amyloid (?)			2 (3.8%)	2 (0.9%)

* Only 8 of these were absolutely proved; 2 were presumptive.

How close a connection exists between these exudates, especially purulent exudates, and pleuropulmonary fistulae or perforations, a connection which Bard (6) and others believe to be very close, is not indicated by our figures. Demonstrable bronchial communication (by manometric or

dye tests) was determined in less than 2 per cent of exudate cases occurring with a satisfactory pulmonary collapse, compared with 13.5 per cent of exudate cases associated with imperfect collapse. This suggests that, if communications or fistulae existed in the former group, they were smaller or more or less occluded. The single "satisfactory collapse" case with demonstrable bronchopleural fistula had a large right apical cavity which had gradually collapsed, but which, for some reason difficult to explain, opened up again and finally broke through, with acute symptoms of sepsis and a fatal termination. Not all perforation cases,

TABLE 13

Complications occurring in "desperate last resort" cases (59) under pneumothorax treatment

	SATISFACTORY COLLAPSE (9)	INCOMPLETELY EFFECTIVE COLLAPSE (36)	TEMPORARY OR UNDETERMINED COLLAPSE (14)	SUMMARY (59)
Pleurisy, exudative	7 (77.8%)	15 (41.7%)	3 (21.4%)	25 (42.4%)
Severe forms	6 (66.7% or 85.7% of exudative)	14 (38.9% or 93.3% of exudative)	3 (21.4% or 100% of exudative)	23 (38.0% or 92% of exudative)
Purulent forms	2 (22.2% or 28.5% of exudative)	6 (16.7% or 40% of exudative)	2 (14.3% or 66.7% of exudative)	10 (17.5% or 40% of exudative)
Septic forms	1 (11.1% or 14.3% of exudative)	2 (5.6% or 13.3% of exudative)	2 (14.3% or 66.7% of exudative)	5 (8.7% or 20% of exudative)
Demonstrable bronchopleural fistula	0	4 (11.1% or 26.7% of exudative)	2 (14.3% or 66.7% of exudative)	6 (10.6% or 24% of exudative)
Tuberculoma or sinus of chest-wall				
Pleurisy, contralateral	0	2 (5.6)%	0	2 (3.4%)
Visceral or generalized tuberculosis	1 (11.1%)	6 (16.7%)	0	7 (11.9%)

however, showed secondary pyogenic infection, and several cases of pyogenic infection were never proved to have bronchial communications. Sixty per cent of demonstrable perforations occurred in "desperate last resort" cases, which made up less than 30 per cent of cases actually under pneumothorax. That is, more than twice the normal proportion of these grave complications occurred in this group, and about four times as many in proportion to numbers as in the rest. A glance at the proportion of serious complications in this group (shown in table 13) is

sufficient to refute loose statements that these are as likely to occur in one pneumothorax case as another. Tuberculous swellings, abscesses or fistulae of the chest-wall occurred in one-third to one-half of the cases with purulent exudates, and nearly always along the site of the needle-puncture or punctures. Contralateral exudative pleurisies were exceptional, occurring in about 1.5 per cent of the cases.

Extrapulmonary tuberculous foci were found to develop during the course of treatment in 6.4 per cent of cases, intestinal lesions being the most common. They occurred most frequently in acute phthisis, as would be expected. It is curious to note that tuberculous meningitis developed more frequently in the "satisfactory collapse" group than in those with an imperfect collapse.[4] The reverse was true of enteritis, as would be expected, because of persistently bacillary lesions favoring infection through the mucosa by swallowed sputum. The figures as to enteritis must be regarded as very inexact, because few of the patients underwent roentgenographic examination of the intestinal tract, and because during the latter part of the period covered we were more ready to diagnose intestinal complications than previously.

The two cases of "accident or untoward reaction" need some comment. One of these had a marked mediastinal displacement, causing respiratory and circulatory embarrassment. It was customary for him to walk from his bed to the operating room and back. On one of these occasions, shortly after returning from a refill, he collapsed and became cyanotic, and was dead by the time a physician reached him. It is thought that he died from acute cardiac dilatation. The other patient, a woman, had previously had pneumothorax on one side, but the lung had been allowed to expand because of progression of disease in the other lung. She was dyspnoeic and had a very low vital capacity, but it was decided to try to induce pneumothorax on the now active side. After 200 cc. of air had been introduced the patient had symptoms of acute suffocation, which were aggravated after an hour's observation and the air had to be removed. The only instances of so called "pleural reflex" or "pleural shock" observed were syncopal attacks, usually following a painful puncture or subsequent pleuritic pains, or prolonged manipulation, or apprehension. None of these were considered serious enough to record. There was also one case of acute cocaine poisoning due to the use of too strong a solution in anaesthetization. No cases of air embolism occurred in this series and only twice in our experience has it ever occurred.

[4] But 3 of the meningitis cases were reported some time after the patients had left the Sanatorium.

BEHAVIOR OF LESIONS IN THE CONTRALATERAL LUNG

Unfortunately, sufficiently careful observations were not made in all cases to enable us to formulate precise statements. Individual judgment, too, differs considerably in the determination of these lesions, and their extent and activity. Therefore, we have satisfied ourselves by recording merely those cases in which there was undoubted exacerbation or progression, and those in which there was undoubted retrogression or amelioration.

A more careful study of this point from a roentgenographic viewpoint is being made by Dr. J. Burns Amberson, Jr., in connection with his studies on "Healing under Pneumothorax."

TABLE 14

	SATISFACTORY COLLAPSE (93)	INCOMPLETELY EFFECTIVE (107)	TEMPORARY OR UNDETERMINED (18)	TOTAL (218)
	per cent	*per cent*	*per cent*	*per cent*
Progressive contralateral lesion....	12 (12.9)	36 (33.6)	6 (33.3)	54 (24.8)
Improved contralateral lesion.....	14 (15.1)	2 (1.9)	0	16 (7.3)

TABLE 15

	ACUTE PHTHISIS (23)	SUBACUTE, SUBCHRONIC OR INTERMEDIATE (142)	CHRONIC FORMS (53)	TOTAL
	per cent	*per cent*	*per cent*	
Progressive contralateral lesion.....	9 (39.1)	36 (25.3)	9 (17.0)	54
Improved contralateral lesion.....	1 (4.3)	12 (8.5)	3 (5.7)	16

Progression of the contralateral pulmonary lesion was recorded in 28 of the "desperate last resort" cases under pneumothorax (49.1 per cent) and improvement in only a single case.

Table 14 shows that when a satisfactory collapse was obtained approximately 15 per cent of the cases showed contralateral improvement, irrespective of the extent or nature of the original lesion there, and 13 per cent had progression or exacerbation. It is to be presumed that in the other 72 per cent little change occurred. When collapse was imperfect, contralateral progression or exacerbation occurred in one-third of the cases. Considered from the point of view of the clinical course of the disease, about 40 per cent of the acute cases showed contralateral progression or exacerbation, 25 per cent of the subacute or subchronic,

and 17 per cent of the chronic. Of all cases it appears that about 25 per cent showed progression in the contralateral lung and 7 per cent improvement, leaving about 68 per cent, or two-thirds, in which there was presumably little change. We have not been able to obtain sufficiently accurate information in the case of the "operative failures" to record the proportion of contralateral extensions. In many of these

TABLE 16

Final disposition of cases treated and reasons for discontinuing pneumothorax

	SATISFACTORY COLLAPSE (93)	INCOMPLETELY EFFECTIVE COLLAPSE (107)	TEMPORARY OR UNDETERMINED COLLAPSE (18)	TOTAL (218)
	per cent	*per cent*	*per cent*	*per cent*
I. Pneumothorax continued after discharge	19 (20.2)	12 (11.2)	0	31 (13.8)
II. Pneumothorax terminated				
1. Optionally: reëxpansion permitted	39 (41.5)	2 (1.9)	0	41 (18.3)
2. By obliterative adhesions or contraction of space	22 (22.2)	29 (27.1)	1 (5.6)	52 (23.8)
3. By massive exudate	2 (2.2)	2 (1.9)	2 (11.1)	6 (2.8)
4. By empyema or ruptured lung	5 (5.4)	11 (10.3)	2 (11.1)	18 (8.3)
a. followed by death	2 (2.2)	4 (3.7)		6 (2.8)
b. followed by thoracic surgery	2 (2.2)	3 (2.8)		5 (2.3)
c. followed by pachypleuritis and adhesions	1 (1.1)	4 (3.7)	2 (11.1)	7 (3.2)
5. By progression in opposite lung	13 (13.8)	25 (23.3)	4 (22.2)	42 (19.3)
6. By uncertain or unsatisfactory clinical response	2 (2.2)	42 (39.2)	11 (61.1)	55 (25.2)
7. By serious extrapulmonary complications	2 (2.2)	2 (1.9)	1 (5.6)	5 (2.3)
8. By severe reactions	3 (3.2)	2 (1.9)	1 (5.6)	6 (2.8)
9. By accident or death	0	7 (6.5)	1 (5.6)	8 (3.7)
10. By patient's refusal or departure	6 (6.4)	10 (9.3)	0	16 (7.3)

cases our records merely state "disease progressive," without indicating whether in one or both lungs. In this study we have considered only well-marked changes in the lesion which were more than transitory. It must be added that some of the progressions in pneumothorax cases occurred quite late, following initial improvement, and that some of these progressions were later checked and became quiescent. These have been included, and account in part for the rather high figures.

Table 16 shows the frequency with which different factors entered into the ultimate outcome of the pneumothorax treatment in each group of cases and in the entire series. Many of these factors overlapped or coexisted, but to attempt to show this in tabular form would complicate matters; hence, the combined incidence of all the factors totals much more than 100 per cent.

In the "satisfactory collapse" group over 40 per cent were optionally discontinued and pulmonary expansion permitted to occur, in the opinion that sufficiently durable healing had occurred to make this procedure reasonably safe. For the combined total this optional discontinuance of treatment was pursued in slightly less than 20 per cent. Pneumothorax was continued after discharge in about 20 per cent of the "satisfactory collapse" group. This leaves about 40 per cent of these that had to be terminated for some necessary reason. Among these reasons in this particular group "obliterative adhesions" and contraction of the pleural space stand foremost, well ahead of progression in the opposite lung, which is the next most frequent reason. In the "incompletely effective collapse" groups, on the other hand, roughly 40 per cent were discontinued because of "unsatisfactory clinical response," nearly always directly dependent on the poor collapse. "Obliterative adhesions" takes second place in this group, and progressive contralateral disease third, both in the neighborhood of 25 per cent. Grave pleural complications account for about 10 per cent of discontinuances in this group, double the figures for the "satisfactory collapse" group. In a comparatively small proportion of all cases treatment was discontinued because of the patient's departure or unwillingness to submit. With proper selection and preliminary explanation to patient or family this factor should occupy a minor place. Serious extrapulmonary complications, *per se*, were responsible for discontinuance in very few cases. Proper selection and judgment also minimize these.

It was deemed of interest and value to study in particular the "optionally discontinued" group, and this will be referred to further on.

FATE OR STATUS OF PATIENTS TWO TO FOURTEEN YEARS AFTERWARD: LOSS OF TUBERCLE BACILLI FROM SPUTUM: "CLOSURE" OF OPEN CASES

With the aid of a very comprehensive follow-up enquiry system, early instituted at Loomis Sanatorium under the direction of an expert statistician and carried on by a worker trained by him until the latter's

recent death, it has been possible to obtain the information desired in nearly all instances. For this follow-up the same questionnaires were used as have been in use for all ex-patients, information being derived directly from the patient when possible, and otherwise from relatives, friends or attending physicians, and checked up by a member of the sanatorium medical staff (not the author) and tabulated by the statistician.

The term "condition satisfactory" means that the patient is either following his or her normal occupation, or not living under conditions of invalidism. It is, however, compatible with some modification or regulation of living or working conditions, and considerable latitude has been allowed in the case of housewives living at home, provided they were without symptoms. The term "under treatment" is applied to patients still receiving pneumothorax treatment and not discharged as patients at the time our enquiry was terminated, July 1, 1925. In a few cases in which the patient was known or reported to be living, but details as to present conditions were insufficient to form conclusions, the term "condition uncertain" has been used. The term "untraced" is self-explanatory.

In the matter of disappearance of tubercle bacilli from the sputum, we have been guided by the results of examination of concentrated specimens, examinations which were performed only after three consecutive examinations of direct smears (except in those cases that had previously shown results on concentration). If the results of examination of one or more concentrated specimens were negative, the case was so recorded, but if later positive results were again obtained we have termed it "temporarily negative," in contrast to those remaining so during observation.

In table 17 the first obvious fact that arrests our attention is the influence of the sort of collapse on the patient's subsequent survival and status. Over 60 per cent of those who achieved a satisfactory collapse were living two to fourteen years later, approximately twice the proportion (30 per cent) of those with an incompletely effective collapse, while 45 per cent were reported in satisfactory condition, approximately five times the proportion (9 per cent) of those with a poor collapse. The "incompletely effective" group shows little obvious advantage over the "operative failures" (pneumothorax impossible), of whom 23 per cent were living and 15 per cent reported in satisfactory condition. The small group with "temporary or undetermined collapse" shows the poorest

TABLE 17

Status of patients of all groups as determined July 1, 1925

	SATISFACTORY COLLAPSE (92)			INCOMPLETELY EFFECTIVE COLLAPSE (106)			TEMPORARY OR UNDETERMINED COLLAPSE (18)			ALL COLLAPSE GROUPS (216)			OPERATIVE FAILURES (67)		
	Number of patients	Per cent		Number of patients	Per cent		Number of patients	Per cent		Number of patients	Per cent		Number of patients	Per cent	
Living	56	60.9	*Per cent of living*	32	30.2	*Per cent of living*	2	11.1	*Per cent of living*	90	41.7	*Per cent of living*	13	22.8	*Per cent of living*
Condition satisfactory	41	44.6	73.2	9	8.5	28.1	1	5.6	50	51	23.6	56.7	6	15.3	46.1
Condition unsatisfactory	5	5.4	8.9	14	13.2	43.8				19	8.8	21.1	6	15.3	46.1
Condition uncertain	7	7.6	12.5	3	2.8	9.3				10	4.6	11.1	1	1.8	7.8
Under treatment	3	3.3	5.4	6	5.7	18.6	1	5.6	50	10	4.6	11.1			
Dead	28	30.5	*Per cent of dead*	70	66.0	*Per cent of dead*	14	77.8	*Per cent of dead*	112	51.4	*Per cent of dead*	42	73.7	*Per cent of dead*
From pulmonary tuberculosis	16	26.1	85.7	57	60.4	91.4	14	77.8	100	87	47.2	91.1	41	71.9	97.6
From related complications	8			7						15					
From perforation of lung	1			>4	3.8	5.7				6	2.8	5.4			
From septic pleurisy	1														
From tuberculous meningitis	4	4.4	14.3	1	0.9	1.4				5	2.3	4.5			
From enteritis and peritonitis	1			2	1.9	2.9				3	1.4	2.7			
From nephritis (amyloid?)	1									1					
From nontuberculous causes	4	4.4	14.3	6	5.7	8.6				10	4.6		1	1.8	
Alcoholism	1											8.9			2.4
Accident	1														
Cardiac failure:				1											
Lobar pneumonia	1														
Influenza:				1											
Postoperative	1			2											
Uncertain	1			2											
Untraced	8	8.7		4	3.8		2	11.1		14	6.9		2	3.5	

results of all, but these, as has been shown, were mostly unusually poor risks. If these are omitted, the largest proportion of deaths (almost 75 per cent) occurred among the "operative failures," two and one-half times the proportion in the "satisfactory collapse" group, and practically all from pulmonary tuberculosis; whereas an appreciable proportion (15 per cent) of deaths in the "satisfactory collapse" group was from non-tuberculous causes, such as accident, alcoholism and acute infections. In the "satisfactory collapse" group one-third of the tuberculosis deaths are attributable to "related complications," including 2 pleural, 4 meningeal and 2 abdominal. The taking off of between 4 and 5 per cent of these patients, otherwise doing well, by the development of tuberculous meningitis, is one of the tragic episodes that cannot be anticipated.

The possibility of fatal complications directly related to pneumothorax,

TABLE 18

Disappearance of tubercle bacilli from sputum

	SATISFACTORY COLLAPSE PATIENTS (92)	INCOMPLETELY EFFECTIVE COLLAPSE PATIENTS (106)	TEMPORARY OR UNDETERMINED COLLAPSE PATIENTS (18)	ALL TREATED PATIENTS (216)	OPERATIVE FAILURES (57)
	per cent	*per cent*		*per cent*	
Temporary disappearance.....	13 (14.1)	4 (3.8)		17 (7.9)	
			per cent		
Permanent disappearance.....	66 (71.7)	7 (6.6)	2 (11.1)	75 (34.7)	
					per cent
Total.....	79 (85.8)	11 (10.4)	2 (11.1)	92 (42.6)	2 (3.5)

while it must be envisaged, is seen to be much less than is often supposed. In all the collapse groups combined slightly over 5 per cent died as a result of pleural complications, perforation of the lung being the chief factor. In all these groups combined 42 per cent were living (twice the proportion among "operative failures") and 24 per cent in satisfactory condition (one and one-half times the proportion for those in whom pneumothorax was impossible).

From table 18 it appears that, when a satisfactory collapse of the lung was obtainable, over 85 per cent of patients lost their bacillary sputum, over 70 per cent remaining nonbacillary during the remainder of the period of observation, or up to their discharge from the Sanatorium. This is one of the most striking favorable results brought about by pneumothorax treatment. The patients in the "incompletely effective

collapse" group showed only about 10 per cent disappearance of bacilli, with only 6.6 per cent permanently free of them, about twice the proportion in the group of "operative failures" (3.5 per cent). Of all patients combined who actually received pneumothorax, a little over 40 per cent lost their bacillary sputum and about one-third remained nonbacillary up to discharge.

RESULTS OBTAINED IN DIFFERENT CLINICAL TYPES OF DISEASE TREATED

It seems worth while to take up separately in groups the clinical types of disease treated, bearing in mind that such separation is not altogether clear-cut.

1: Acute Phthisis, 27 Cases (9.8 per cent)

The previous course in all of these was active and rapidly progressive and the prognosis uniformly unfavorable. Eighteen (66.7 per cent) were "desperate last resort" cases. Twenty-five (92.6 per cent) were classified as having far advanced disease. The general condition was stated as "fair" in only two (7.4 per cent), "much impaired" in fifteen (55.5 per cent), and "impaired" in the remaining ten. The presumable duration of disease was under six months in 20, and over six months in 7.

Degree of Collapse: A satisfactory or effective collapse was obtained in 10 (37 per cent), unsatisfactory or incompletely effective in 9 (33.3 per cent), temporary or undetermined in 4 (14.8 per cent), and 4 (14.8 per cent) were "operative failures," in whom no pneumothorax was possible. Omitting these last, we have 23 treated patients, of whom 21 (91.3 per cent) were traced up to July, 1925. Of these, the end-results were:

		per cent
Total living	5	(23.8)
Dead of tuberculosis or complications	16	(76.2)
Total cases traced	21	(100.0)
Condition satisfactory	2	(9.5)

Of 10 in whom satisfactory collapse was obtained, 8 were traced to July, 1925. Of these the end-results were:

		per cent
Living	4	(50)
Dead of tuberculosis or complications	4	(50)
Condition satisfactory	2	(25)
Condition partly satisfactory	1	
Still under treatment	1	

Contralateral progression of disease during treatment occurred in 9 cases, including 30 per cent of those with satisfactory collapse and 44.4 per cent of those with unsatisfactory or poor collapse.

2: Subacute, Subchronic or Intermediate Forms, 160 Patients, 162 Cases (58.9 per cent)

Of these, 48 (30 per cent) were considered "desperate last resort" cases, and 133 (82.1 per cent) were classified as having far-advanced disease. The presumable duration of disease varied greatly; in the "satisfactory collapse" group the average was lowest, and in the "operative failure" group highest. It should be mentioned that two patients are included who underwent acute exacerbations of longer-standing disease prior to treatment.

Degree of Collapse: A satisfactory or effective collapse was obtained in 71 cases (43.8 per cent), unsatisfactory or incompletely effective in 61 cases (37.5 per cent), temporary or undetermined in 10 (6.2 per cent), and pneumothorax was impossible in 20 (12.5 per cent). Omitting these last, we have 140 treated patients, of whom 132 (94.3 per cent) were traced up to July, 1925. Of these, the end-results were:

		per cent
Living	64	(48.5)
Dead	68	(51.5)

Of those dead, 65 (95.6 per cent) died of tuberculosis or related complications.

Of those living, the status was as follows:

Condition satisfactory, 39 (60.9 per cent), or 29.5 per cent of all traced.

Condition unsatisfactory, 14 (21.9 per cent), or 10.6 per cent of all traced.

Doubtful or under treatment, 11 (17.2 per cent), or 8.3 per cent of all traced.

3: Very Chronic Forms, 86 Patients or Cases (31.3 per cent)

Of these, 24 (27.6 per cent) were considered "desperate last resort" cases and 79 (91.9 per cent) were classified as having far-advanced disease. The presumable duration of disease was over two years in 70 (81.4 per cent).

Degree of Collapse: A satisfactory or effective collapse was obtained in only 13 cases (15.1 per cent), and in 33 (39.2 per cent) pneumothorax

was entirely impossible. A comparison of the treated cases with these controls shows the following results:

	CHRONIC PHTHISIS, WITH PNEUMOTHORAX	CHRONIC PHTHISIS; PNEUMOTHORAX IMPOSSIBLE
Patients traced	49	31
Living	19 (38.8 per cent)	10 (32.2 per cent)
Condition satisfactory	8 (16.3 per cent)	4 (12.9 per cent)
Dead	30 (61.2 per cent)	21 (67.8 per cent)
Of tuberculosis or complications	27 (55.1 per cent or 90 per cent of deaths)	21 (67.8 per cent, or 100 per cent of deaths)

This comparison shows but a slight advantage for the pneumothorax group, although, of course, the comparative length of life of those dying has not been compared, and the results in the "satisfactory collapse" subgroup alone are, of course, better, although not striking, 10 patients out of 13 being traced, of whom half were living, but only two reported in satisfactory condition.

It seems obvious that very chronic forms of phthisis do not offer a fruitful field for pneumothorax therapy, and that thoracoplasty should be resorted to when practicable in preference to tinkering along with an unsatisfactory pneumothorax. The same thing is doubtless true of many of the "incompletely effective collapse" group, and of the "operative failures." As a matter of fact, 7 of the former and 3 of the latter did subsequently have thoracoplasty performed. At the present time many more are being advised to undergo thoracic surgery.

The foregoing study of this series, grouped roughly according to clinical type or course (acuteness or chronicity), appears to show that the greatest proportion of satisfactory pneumothoraces, as well as the best end-results, occurred in the subacute or subchronic "intermediate" group. This agrees very well with the clinical judgment of most careful observers and workers. In round numbers, 44 per cent of this group obtained a satisfactory or effective collapse and in only 20 per cent was pneumothorax impossible or "temporary." Approximately 50 per cent of patients traced, who received any pneumothorax treatment, were alive and 30 per cent reported in satisfactory condition.

The small group of "acute phthisis" comprised almost all very ill patients, as would be expected. "Operative failures" and "temporary or undetermined collapse" cases together made up 30 per cent. The final showing of approximately 25 per cent living and 10 per cent in

satisfactory condition, among patients receiving any pneumothorax treatment, is not highly encouraging, but it must be recalled that probably all of these would have died under ordinary circumstances. If we consider only the small subgroup in which an effective collapse was obtained, the results are distinctly better, showing half of those traced to be alive and 25 per cent in satisfactory condition. Thus, therapeutic pneumothorax should not be ruled out in acute phthisis, unless the disease is manifestly progressing in both lungs or the prognosis obviously hopeless for some other reason. While, in general, the results are discouraging, there are sufficient exceptions to justify, or even demand, a trial of this measure, in predominantly unilateral, acute cases.

The case is quite different with very chronic phthisis, in which there is such slight advantage of those receiving pneumothorax over the "operative failures" as to raise the question of whether very much was accomplished.

"Desperate Last Resort" Cases

It has seemed worth while to take up separately this group of 88 patients or cases. Only 9 (10.2 per cent) secured a satisfactory or effective collapse, 36 (40.9 per cent) an incompletely effective one, 14 (15.9 per cent) a temporary or undetermined one, and in 29 (33 per cent) pneumothorax was impossible. Twenty-five per cent were complicated at the time of beginning treatment with tuberculous enteritis and at least 10 per cent with tuberculous laryngitis. Posthaemorrhagic pneumonia had already begun in 5.7 per cent. Three had diabetes and one syphilis. Serious complications occurred with great frequency during treatment, as mentioned. Progression of the disease in the contralateral lung is recorded in half the cases under pneumothorax treatment and may have occurred in more. The final status is shown in table 19.

TABLE 19

Results in "desperate last resort" group

	TOTAL NUMBER	LIVING	DEAD	UNTRACED	IN SATISFACTORY CONDITION	DEAD OF TUBERCULOSIS OR COMPLICATIONS
		per cent	*per cent*	*per cent*	*per cent*	*per cent*
All patients receiving pneumothorax.....	59	7 (11.9)	49 (83.1)	3 (5.0)	4 (6.8)	46 (78.0)
Patients with satisfactory collapse.....	9	3 (33.3)	6 (66.7)	0 0	3 (33.3)	6 (66.7)
Pneumothorax impossible...	29	1 (3.5)	27 (93.0)	1 (3.5)	0 0	27 (93.0)

Table 19 shows that the results, as a whole, were very unsatisfactory, but distinctly better in the group receiving pneumothorax than in the "operative failure" group, and 33 per cent satisfactory in the small group in which an effective collapse was obtainable. If we now consider the length of life of those patients who died in each group, the contrast is strengthened (table 20).

TABLE 20

Length of life of patients dying in "desperate last resort" group

	SATISFACTORY COLLAPSE	INCOMPLETELY EFFECTIVE COLLAPSE	TEMPORARY OR UNDETERMINED COLLAPSE	OPERATIVE FAILURES
6 months or less	1	15	4	10
7 to 12 months		3	6	8
1 to 2 years	2	8	4	3
2 to 3 years	1	2		1
3 to 4 years	1	3		2
4 to 5 years				
5 to 6 years				
6 to 7 years	1			
Uncertain				3
Average length of life.....	33.3 months	13.9 months	10.5 months	10.1 months

The average duration of treatment was only 12.6 months for those with "satisfactory or effective collapse," 6.3 months for those with an "incompletely effective collapse," and 1.5 months for those with "temporary or undetermined collapse."

It seems reasonable to conclude from analysis of this group of patients that, while "desperate last resort" cases rarely achieve lasting results and are undesirable subjects for therapeutic pneumothorax from a number of standpoints, the palliative results were nevertheless not inconsiderable, some patients undergoing temporary amelioration and prolongation of life. Hence, humanitarian considerations will not allow us to reject all such cases because they are poor risks. It will often be a matter of very nice clinical (and humanitarian) judgment whether to try pneumothorax in a case of this sort, and it seems that, in justice to both professional reputation and that of the method, the probably unsatisfactory nature of the results should first be explained, preferably to a sensible relative, but in some cases to the patient himself. The best way to avoid such dilemmas is not to delay pneumothorax until the patient gets into this group.

Patients in Whom Treatment Was Optionally Discontinued

There were 41 of such cases in this series, all but two belonging to the "satisfactory or effective collapse" group. All except these two had lost their bacillary sputum for many months. The clinical response appears to have been satisfactory in the case of all but one patient, whose condition had remained about stationary. Expansion of the collapsed lung under observation occurred in 33 of these patients. The duration of pneumothorax treatment had been as follows:

6 to 12 months in 8	25 to 36 months in 4
13 to 24 months in 28	37 to 48 months in 1

Their average duration of pneumothorax treatment was 19.2 months. The stage of their disease on beginning treatment was as follows:

		per cent
Moderately advanced	15	(36.6)
Moderately advanced (P), Far advanced (R)	5	(12.2)
Far advanced	21	(51.2)

The status of these patients, as determined July 1, 1925, was as follows:

		per cent
Living	32	(78.0)
Dead	5	(12.2)
Untraced	4	(9.8)

Of those living, 24 were reported in satisfactory condition (58.5 per cent of entire group, 75 per cent of those living) and 3 in unsatisfactory condition, in 3 the condition was undetermined, and 2 were under treatment, their condition probably being unsatisfactory. Thirteen in all, or 31.7 per cent, were considered to have relapsed since stopping treatment.

It appears from the above figures that in a fairly considerable group of patients in whom pneumothorax had been effective, and among whom were included a larger proportion of cases of moderately advanced disease than in any other groups, pneumothorax treatment was optionally discontinued and reëxpansion of the lung permitted (under observation in the majority), and that in the majority of instances subsequent events justified this decision; that, however, 32 per cent of relapses did occur, and that about 12 per cent eventually died from tuberculosis. These findings give us cause for both caution and encouragement. They do show, most certainly, that the old dictum "once pneumothorax, always

pneumothorax," is far from true, and they also suggest that if the disease were not allowed to become too far advanced and destroy too much pulmonary tissue before instituting pneumothorax, a larger proportion could eventually obtain both healing and reëxpansion.

SUMMARY AND CONCLUSIONS

1. A series of 273 patients (275 cases) at the Loomis Sanatorium, in whom therapeutic pneumothorax was administered or attempted during the years 1911–1923 inclusive, is reported, with particular attention to the end-results as determined up to July 1, 1925, with the aid of a comprehensive follow-up system for discharged patients. Fairly definite and reliable information is available for nearly 95 per cent of these patients.

2. From 1918 on, about three times as many admitted tuberculosis patients as formerly have received this treatment and for longer periods. In the earlier group extremely unfavorable cases predominated and a satisfactory collapse was less often secured.

3. The entire series contains at least 85 per cent of cases of far-advanced disease and 32 per cent of "desperate last resort" cases. Classified according to clinical type or course, there were about 10 per cent of acute phthisis, 30 per cent of very chronic forms, and 60 per cent more or less intermediate, subacute or subchronic. Almost all could be regarded as clinically active, and all had symptoms or disability of some sort, dependent on their tuberculosis.

4. About one-third of all in whom this procedure was attempted obtained a satisfactory or effective collapse of the diseased lung, and in about 20 per cent it was found impossible to induce any pneumothorax whatsoever. In the remainder, various degrees of collapse, more or less effective or temporary, were obtained. Extremely chronic cases and "desperate last resort" cases are unlikely to obtain a satisfactory collapse. On the average the shorter the duration of symptoms the more likely is an effective collapse to occur, but exceptions happen frequently, and very acute cases are more likely to be associated with extensive pleuritic adhesions than the less acute and florid ones of the "intermediate" group.

5. Patients with a satisfactory or effective collapse continued treatment, on the average, nearly twice as long as those with an incompletely effective one, and practically all the "optionally discontinued," in whom

the lung was allowed to reëxpand, because considered healed, were in this group. Those with "temporary or undetermined collapse" were treated, as a rule, for exceedingly brief periods. Among the various reasons for discontinuing pneumothorax, obliterative adhesions with contraction of the pleural space played an important rôle, also unsatisfactory clinical response, due in most cases to an ineffective or incompletely effective collapse. The term "effective collapse" must be differentiated from "total collapse," as the two are not synonymous. Progression or exacerbation of disease in the contralateral lung was a somewhat less frequent reason than the foregoing for the cessation of treatment, but not uncommon, assuming great importance in the "desperate last resort" cases, as well as in the group of acute phthisis.

6. Pleuritic complications were encountered in at least half of those treated by pneumothorax, serous pleurisies being most common. The more serious complications were most frequently associated with the more serious types of disease and those in which pathological conditions prevented a satisfactory collapse. Severe pleurisies (accompanied by more than slight or transitory constitutional or functional disturbance) occurred in nearly one-third of all cases, and for the "satisfactory collapse" group alone the figures were the same. Purulent pleurisies occured in 11.5 per cent of all cases, but less frequently in those with satisfactory collapse. Septic pleurisies and demonstrable bronchopleural fistula (evidence of perforation of the lung) occurred in not quite 5 per cent of all cases. While septic infection occurred in the same proportion of "satisfactory collapse" cases, it was less serious, bronchopleural fistula being demonstrated in only one of this group.

7. Of other important complications developing during or after the course of treatment, intestinal were most frequently noted, in about 4 per cent. Tuberculous meningitis occurred in over 4 per cent of the "satisfactory collapse" group, being of course fatal. In some cases it developed long after the patient's discharge. There were no cases of gas embolism nor serious "pleural reflex or shock." The latter term is so indefinite, and serves so often to cover ignorance of what has happened, that he who uses it should be challenged to "show cause."

8. Progression or exacerbation of disease in the contralateral lung has been recorded in about 25 per cent of cases under pneumothorax, and improvement in about 7 per cent, leaving about two-thirds *in statu quo*. As only a minority of cases were clinically unilateral this is not a bad showing. Among the "satisfactory collapse" group alone more showed improvement in the contralateral lung than the reverse.

9. The results obtained vary greatly with certain factors, most important of which is the obtaining and maintaining of a satisfactory collapse of the diseased areas for a sufficient period of time. The proportion of apparently durable end-results appears to bear a very close relation to the permanent disappearance of tubercle bacilli from the sputum. This corresponds to what has often been observed in studies of large series of patients, such as those of King (7), Bardswell (8) and Guinard (9). Among all our pneumothorax-treated patients tubercle bacilli permanently disappeared under observation in approximately 35 per cent, and not quite 25 per cent remained in satisfactory condition at the end of two to fourteen years, 42 per cent being alive. In the "satisfactory collapse" group alone, 72 per cent obtained a persistently negative sputum under observation and 45 per cent remained in satisfactory condition, over 60 per cent being alive at the end of two to fourteen years.

10. Of all patients in whom any pneumothorax at all was induced, 42 per cent were living at the end of two to fourteen years, and 24 per cent were reported in satisfactory condition. Of the group with satisfactory collapse, 61 per cent were living, and 45 per cent were reported in satisfactory condition. On the other hand, of those patients in whom pneumothorax was impossible, 23 per cent were living, and 15 per cent were reported in satisfactory condition. That is, the end-results in the pneumothorax group were nearly twice as good as when no pneumothorax was possible. Actually the "satisfactory collapse" group accounts for most of the difference: when a satisfactory collapse was obtained the chances of being alive after two to fourteen years were almost trebled, and the chances of being in satisfactory condition exactly trebled. Patients with disease of very chronic type showed the least striking results and were exceptions to the above. Doubtless, for many of these and of the "incompletely effective collapse" group, thoracoplasty should be preferred.

11. The striking effect of a satisfactory pneumothorax in bringing about the disappearance of tubercle bacilli from the sputum is obvious and should command attention.

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LIGHT IN THE TREATMENT OF TUBERCULOSIS[1]

E. S. BULLOCK[2]

Back in 1898 we knew that diffuse daylight, as well as direct sunlight, would kill tubercle bacilli if sufficient exposure was allowed. We also understood that light is Nature's universal antiseptic, and that, while necessary to many forms of life, it is at the same time detrimental to some and deadly to others. Only later did we learn that it is very essential to the proper growth and development of young animals of many species, including man. That it is not absolutely necessary after growth is attained is proved by the fact that, during the Middle Ages particularly, many men endured imprisonment in dark dungeons for years, occasionally almost a life-time, with no special impairment of health. Mules, too, have remained in the darkness of coal mines as long as twelve years in healthy condition and without a lowering of the haemoglobin content of the blood.

My interest in light as applied to disease, particularly tuberculosis, began about thirty years ago, and has continued more or less ever since. At that time an Army physician on duty in the Philippines reported that he had obtained good results in lessening the incidence of dysentery among our soldiers by having them wear red-flannel abdominal binders while on duty in the tropics. It was this that aroused my interest in light, and I wondered how much light really penetrated the body, and, if it did penetrate, could it account in a measure for the results achieved in the treatment of tuberculosis in the brilliant sunlight of our Southwestern United States.

At that time I was on duty at Fort Bayard, New Mexico, which Surgeon-General Sternberg had recently converted into a sanatorium for tuberculous soldiers. It was during and just after the Spanish War,

[1] Read at a meeting of the Trudeau Society of Michigan, Lansing, Michigan, October 17, 1927.

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when large numbers of soldiers became actively tuberculous, and Fort Bayard increased from one patient in October, 1898, to 1,500 two years later. Many of these men were much impaired physically, not only by tuberculosis but with dysentery and malaria as complications. The death-rate among them was terrible, and, as I made all the postmortems, I had an abundance of material for trying anything that occurred to me as worthwhile. At one time there were in the dead-house the bodies of four white men and three black negroes. We had then only the oldfashioned sixteen-candle-power carbon-filament light for supplying illumination at Fort Bayard. I buried such a lamp deep in the chest cavities of all these bodies, and carefully sewed them up so that only the wires protruded. Then, darkening the room, the current was applied, and in the four whites the chest was quite well illuminated, but in the blacks there was relative failure to light the chest.

The conclusion seemed to be inevitable that a certain kind of light can reach the interior of white men, and equally as plain that it penetrates the skin of black men hardly at all. The light too employed in this experiment consisted mostly of long yellow rays, with a penetrating power thousands of times as great as any short or ultraviolet rays, which are so readily absorbed by many substances and transmitted completely by none.

From this it follows, about as conclusively, that the black races are pigmented in order to keep light out, a protective coloring in the full sense of that expression. We now know that the blacker the skin the more perfect the absorption of all rays, particularly the short ultraviolets about which we hear so much nowadays.

It follows that even sunlight must carry with it a harmful or lethal influence, or the black pigment would not be there to keep it out, or rather absorb and convert it into some other form of energy. In the tropics the sunlight day is twelve hours long at all times of the year; that is, there are twelve hours of possible sunshine, barring its absorption by moisture and dust. With this extreme exposure all tropical races must have a good protective coloring to convert the active light into something harmless; colloquially speaking, to "keep it out."

Thirty years ago not much was understood about the chemical or ultraviolet rays, though sunlight therapeutically had been used as long as there is any history at all, and Antyles, a Roman physician, successfully treated rickets by means of sun-baths, and the use of red light in

smallpox dates from the thirteenth century. During the same century smallpox was treated by the exclusion of all light. In 1742 Harris observed that ground-up clam shells, which had been exposed to the sun for a long time, were beneficial in the treatment of certain diseases. The treatment of tuberculosis of the bones and joints by means of sunlight dates from 1840, when the results were published. There was a special sun clinic in Austria in 1855. These few historical facts are mentioned to impress the fact that there is nothing new about sun treatment.[3]

In actual knowledge of the physics of light the most important observation was made by Grotthus in 1819, when he laid down the law that only absorbed rays can produce photochemical change.

By 1800 William Herschel knew that the greatest heating effect was beyond the red end of the visible spectrum, and in 1840 John Herschel found that the spectrum did extend beyond the visible part and that the Fraunhofer lines continue beyond the visible spectrum. In 1803, working with silver chloride, Inglefield suggested the existence of radiations beyond the violet end of the spectrum,—thus the discovery of infraviolet rays which shortly followed. It was Charcot in 1858 who recorded that the chemical rays must be the active portion of the spectrum. In 1899 Widmark of Sweden was the first to prove that sunburn is not due to heat rays, but rather to the cold light at the other end of the spectrum,—the blue, violet and ultraviolet. The sources of chemical light that are effective, and which carry much greater proportions of the light at the left and beyond the left end of the spectrum than even the sun, are all inventions of the past forty years, and quartz is employed because it transmits these rays with less absorption than any other known substance, one thousand times better than glass. The important thing to remember in this brief resumé is that we now have at our command sources of chemical light much more potent than the sun.

Even thirty years ago the exceeding complexity of light was not fully understood, or that its study would open a whole new field of investigation, especially as regards its effects on living things and their correct interpretation, most of which, we must admit, still lies in the future. Even though these short rays can kill tubercle bacilli in thin smears

[3] For historical and physical facts I am indebted to Mayer's valuable *Clinical Application of Sunlight and Artificial Radiation.*

in a very short time, they do not penetrate the body more than 1.5 mm.,[4] and it is fortunate that they do not, for they would kill the body cells as easily as they do bacteria.

Tanning then must be a protective measure, the main purpose of which is to keep chemical light out of the body by interposing a pigment which will absorb the deadly short rays. If such light were not harmful, Nature would hardly go to so much trouble to keep it out. The deeper the pigmentation the more completely these rays are absorbed and the less they penetrate, and from Grotthus's law we know that all of their effects can only occur as a result of their absorption, not their transmission. In other words, if our bodies, like quartz, were transparent to these rays, they could not affect us. It also follows that the pigment deposited in the skin as a result of exposure to these rays, by being especially adapted to their absorption, protects the deeper structures from their evil influence,—quick to manifest itself, first, by an erythema, and by longer exposure in the unprotected by burns of all degrees up to those which may prove fatal.

During almost all of my medical life I have appreciated the dangers inherent in sunlight and of late years in these added sources of chemical light supplied in the carbon-arc and mercury-quartz lamps which we now have at our command. With their even greater proportion of chemical rays, it stands us in hand to tread warily, until some of the present confusion has been cleared up, and specific indications for their application are better defined. We know that they are bad for smallpox patients and that, more than likely, they account for some of the symptoms of pellagra. Also, certain individuals cannot tolerate summer sunlight without developing skin manifestations which are often quite distressing.

As the study of light progresses it increases in complexity, and the difficulty of coming to definite conclusions is better and better appreciated. Right now it seems to me timely that some one gave a warning and that an attempt to clarify the subject should be made, so that we may at least stay on the safe side in the clinical application of these rays, and, above all, that our sanity in their use is maintained, and that as a profession we are not carried on a wave of simple faddism.

What do we actually know that is quite beyond controversy? What can be safe landmarks in further exploration?

[4] Recent investigations show that short rays do reach the blood-vessels of the skin in the unpigmented body.

These radiations come to us, at least as we apply them in practice, from three sources, the sun, the carbon-arc, and the mercury-quartz lamp. All the rays coming from the sun can be divided into ultraviolets, 1 per cent, visible light 19 per cent, and heat rays 80 per cent. Compared with certain artificial sources the sun is a poor radiator of ultraviolet rays, but, when it can be used, it is the preferable source, for it costs nothing and contains sufficient ultraviolet for most purposes. The carbon-arc of low amperage is comparatively inexpensive, and is the best all-round substitute for sunlight, which it resembles more closely than light from any other artificial source, and it costs less to operate and maintain. It is, of course, a hot light, but can be successfully used with the patient 15 or 20 feet away, and this makes it possible to expose a larger number of patients at one time,—from thirty to fifty when several of the carbon-arcs are combined in a group, special ventilation being supplied to keep down the temperature of the room as well as to furnish plenty of fresh air. The mercury-quartz lamp has the advantage of being relatively cool, and gives a good proportion of short rays, but it is quite expensive in installation and deteriorates rapidly, losing 50 per cent of its efficiency at the end of six months' operation. It can be used close to the patient. The water light can be employed for the intensive application of ultraviolet rays in such a way as to entirely prevent the passage of the rays through air, which of course absorbs them readily; it is therefore especially useful in skin lesions. The flaming arc gives off radiations rich in ultraviolet light, but the electrodes, made of various substances, including iron, are rapidly consumed, necessitating frequent replacement; all of them are very hot lights and make much noise. As they are perfected, special uses will undoubtedly be found for them.

By and large, the sources mentioned are those most frequently employed therapeutically at present, and are the sources of photochemical light which we may use for the benefit of our patients and which we can abuse, as well, and use to their disadvantage. In fact, if it were not for Nature's pigment-forming capacity, many patients would be seriously injured from the abuse of these rays, but fortunately in most individuals a good coat of tan limits our ability to do harm.

During winter the sun's ultraviolet rays are much diminished, as also when the sun is low on the horizon and the rays must penetrate twice the thickness of atmosphere in order to reach a given point. Places of high altitude, with a dry, clear, thin atmosphere, have a greater propor-

tion of actinic light, for the thicker the atmosphere and the more moisture, smoke and dust it contains, the more these rays will be absorbed by the particulate matter contained in the atmosphere. It is because of this that country districts have more actinic light than cities; particularly industrial cities with their smoky atmosphere. The absence of effective sunlight in winter and in cities is what is popularlizing the use of artificial sources of actinic light.

If sunlight contained a larger proportion of photochemical light than it does, life on the earth would have to develop special protective mechanisms in order to continue. I wish to emphasize, then, the dangers inherent in the use of these deadly rays, and one can hardly be too cautious in their application to human beings.

Methods of estimating the actinic value of light are by no means simple or easy. This is another reason for using the carbon-arc, which approximates sunlight fairly well, for it is practically constant in the amount of ultraviolet given off, and thus does not leave the operator constantly "up in the air" as to what dosage is being used. The radiometer for the measurement of light values is very expensive and must be housed in a special revolving astronomical tower. In the high altitudes of our West and Southwest tables for the different months of the year can be constructed and followed, for the absence of moisture, in the form of fog and clouds, etc., gives a relatively constant actinic content of sunlight for any given period of the year. In such regions sunlight is the source of chemical rays, which will be naturally chosen, for it is available practically throughout the year, and, to repeat, costs nothing.

We have not yet been able to define just how or when the longer heat rays, including the infrared, fit into the light picture. As a matter of fact, there is no good reason for excluding any portion of the visible or invisible spectrum when studying the effects of light. Nor should we conclude that short rays to the left of the spectrum are the only ones of benefit to our patients; especially when we understand the enormous penetrating power of the longer rays which a good coat of tan does not absorb. The infrared rays will penetrate the entire human body, as proved by the raising of the temperature on the distant side. These longer rays (some of them at least) accompany the infraviolet in all our applications of light; least in the mercury-quartz, and most in sunlight. We know that heat rays, up to a certain point, increase an ani-

mal's resistance to infection, and beyond a certain degree, of course, resistance is lowered, and the application of heat becomes detrimental. Some light enthusiasts, now so common, have discovered that they must exclude heat and light carefully unless they wish the formation of an abscess, and, *per contra*, that exposure to these will hasten abscess formation.

Many of the facts recorded here may seem simple, indeed elemental, but there is so much confusion, and light is being used so promiscuously and unscientifically that certainly no harm can be done by accenting them. Among those which should always be borne in mind, and which frequent repetition cannot make out of place, is that in dealing with photochemical light we have in our hands an agent of great potency; we must remember that these rays can kill and cause burns of all degrees of severity, that they may cause reactions in the tuberculous, comparable in every way with tuberculin effects and with all that substance's power of working havoc in the patient. It must constantly be recalled that they must not be used in subjects in which there is no tendency to pigment formation, nor in febrile patients. We now come naturally to the point of the real usefulness of photochemical light and, if useful, how, when, or where. Our knowledge remains too incomplete as yet to permit clear definition of these points, but the real purpose of this paper is an attempt at their classification, as well as a warning.

Let it be recalled that the chemical rays penetrate the body only a very short distance, at the most not over 1.5 mm.,[5] and that they hardly penetrate the deeply pigmented body at all, being all absorbed at the surface; therefore they cannot exercise disinfecting power beyond a very limited depth. With this in mind, Finsen in his work with lupus adopted methods of pressing out the blood and making the lesion as flat as possible,—all in the same plane,—thus giving the rays the best possible chance at the lesion without having to penetrate a layer of air.

We actually know that short rays can cure rickets and tetany, and that light from which these rays are excluded can do no such thing. We know that codliver oil can accomplish the same result. How these agencies do this we do not know. It sounds well to say that they cause mobilization of the calcium or alter internal secretions, but, having so stated, nothing has really been said.

About 1912 the late Dr. David Twichell, then my assistant, and I

[5] See footnote 4.

succeeded in healing primary tuberculous ulcers in tuberculous guinea pigs,—not once but many times,—by means of sunlight applied in increasing doses up to twenty minutes. Of course, the general infection was not changed, and ended in death except in those killed for purposes of study. We found that we could not carry the exposure of the entire animal safely beyond twenty minutes, for a greater time brought on symptoms, first of increasing discomfort, and finally death in about forty-five minutes. This is a very good example, not only of the possible healing power of sunlight, but of its harmful capabilities; and yet I have frequently seen a patient lie hour after hour in hot summer sun (120°F.) with no apparent ill effects, when well pigmented, showing that the long rays are the least to be feared.

We know that in many skin diseases light has proved beneficial and sometimes curative, as in lupus; though in this disease the "disinfection theory" has been abandoned and an explanation sought elsewhere, as it will also probably have to be in healing ulcer in guinea pigs and in laryngeal tuberculosis. On the face it seems to be true that in tuberculosis of the bones, joints and lymphatics, light is useful, but just how much good can be attributed to cool, fresh, moving air, which accompanies the sunbaths, and how much is directly creditable to the light, is at present an unsolved question.

Even diffuse daylight contains photochemical rays, sometimes in lightly cloudy weather even more than in sunlight. Without keeping patients entirely in the dark it is impossible to completely separate the effects of light from those of cool moving air, *airbaths* so called, but it has certainly been shown that, when light is employed in still, unventilated rooms, the effects are not so good. If it is granted that light has usefulness in the treatment of tuberculosis, why not give some of the credit to the entire spectrum, as well as to the chemical rays which Nature so carefully excluded by her tanning process, plus the influences of the associated airbaths? How do we know what now unknown effect may be the result of the longer rays? The very long rays, particularly the infrared, have been found to have very great penetrating power; not even tan will keep them out.

It is my own belief that airbaths are even more essential than exposure to sunlight, or any other source of short rays. This does not apply, of course, in the care of rickets and tetany, in which the chemical rays have been proved necessary, and, for all I know to the contrary, it may be true in some other affections.

About 1910 Rollier's work became well-known, and caused a renewal of my interest in heliotherapy. At the New Mexico Cottage Sanatorium at Silver City, New Mexico, where for many years I was Physician-in-Chief, I tanned all my patients for a period of five years; that is, all who could be tanned and were suitable for treatment. The average color of the patients was a fair approximation of mahogany. I found that patients, afebrile and otherwise suitable, and carefully accustomed to light, got so that they could be in the sun hour after hour, day after day, summer and winter. Of course, it should be recalled that winter days in that crystal-clear atmosphere are quite different from other parts of the United States, and that what is possible there might be quite impossible elsewhere. At this point a word of explanation of what is a suitable case is called for:—patients who will tan well, and are afebrile, and,—an especially necessary point to remember,—those with whom the treatment does not disagree, nor cause an increase of pulse and temperature, and a feeling of lassitude or headache (the head must always be shaded) or febrile reactions. Analysis will disclose that it is the so called productive type of lesion, not the exudative, with which the treatment agrees. Of course, the concomitant airbath which the patients got was an incidental but constant feature of the treatment. In New Mexico, at an altitude of 6,000 feet, it is often possible to use heliotherapy on all but fifteen or twenty days out of a year, at least for a portion of the day.

If there is really something of value in sunlight-air-baths such regions as our Southwestern United States will always have a big advantage over less favored places; and, it seems to me, the conscientious physician will give those of his patients who can afford it such a marked advantage. Only those who are honestly mistaken, or are doctors strictly for what they can get out of it, will keep on saying that one climate is quite as good as another for people with tuberculosis. Certainly, if we had a choice of rooms in a house for a patient ill of tuberculosis, the darkest, most unventilated room would not be chosen. In effect, that is about what is done when the climate of Michigan, for instance, is advocated as the equal of that of New Mexico.

However, to return to the subject of light as applied in my own practice, it must be emphasized that nearly all my work has been done with pulmonary tuberculosis and its commonly associated complications. My cases of bone, joint and lymphatic tuberculosis are much too few for me to have an authorative opinion based on my own knowledge.

I would, however, like to interject a few theoretical considerations on the subject of the last-named tuberculous afflictions, in the treatment of which such dramatic achievements are claimed for heliotherapy. Let us recall, in the midst of all the prevalent enthusiasm for heliotherapy in bone and joint cases, that forty or more years ago Louis A. Sayre of New York taught us how to get good results in such affections; that rest was a pivotal point then, as it is now, in the treatment of all varieties of tuberculosis. Nowadays it seems quite the mode to forget some of the good work that has been done by our predecessors. Many of these lesions are due to the bovine tubercle bacillus, are slow and chronic, and are prone to recover from active symptoms if given a chance. I am sure that in my young days in medicine in New York I saw all the things occur that are now so loudly acclaimed as exclusively due to heliotherapy. The orthopoedists are practically a unit in the opinion that actual cure in bone and joint tuberculosis does not occur. They are just as canny in the use of the word "cure" as is the phthisiotherapeutist. What they do get is "arrest," encapsulation, cessation of activity, and they are suspicious of lasting results in any mobile joint.

The purpose of the Hibbs operation is to get a completely immobile joint in as short a time as possible in a fairly good position. Of course, since Sayre's time a great forward step has been taken in avoiding open operations and to use aspiration when evacuation of pus is necessary. All are agreed upon this point. Of course, restoration of function is a wonderful thing to obtain, but, if it is got at the price of relapse and possibly ultimate destruction of life, much too great a cost has been paid, and the best orthopoedic thought is that such is often the case. Heliotherapy in bone and joint tuberculosis may be a valuable adjunct, but that is all it is, and these cases should not be permitted to drift out of the hands of qualified orthopoedic surgeons into those of the sun-cure extremists.

Practically all are agreed that no such striking results are obtained in pulmonary tuberculosis and, in fact, some think sun-cure actually contraindicated here. If there is a difference, and we attribute better results to heliotherapy in bone and joint cases than in pulmonary types, it is probably due to the essential difference in gravity of the disease, as between infection due to the human and that due to the bovine bacillus, in the former of which there is no such tendency to spontaneous healing as occurs in the latter.

At the end of five years of intensive tanning of my patients I took stock of results. Whenever the subject of statistics comes up we all have a right to be skeptical, and criticize them carefully, taking into consideration who collected them, and all the "whys" and "wherefores" that entered into them. In this connection I can only say that in five years I had about 500 cases, that those studied were genuine tuberculous subjects (sputum positive), all others being carefully excluded, and that exposure to sunlight and air did not give any improvement whatever in my statistics in the three classes of incipient, moderately advanced and far advanced who became bacilli-free under treatment. As compared with the previous ten years the statistics were the same; that is, the old and tried dietetic-hygienic-rest-fresh-air treatment, without sunlight exposures or specially given airbaths, gave as good results. A man's own experience cannot help but mean more to him than to anyone else, but it never becomes effective until many others have had the same experience and obtained the same results.

During the following five years I stopped the use of direct sunlight, and used only airbaths in diffuse daylight,—in other words, keeping the patient stripped in the shade. At the end of five years again a study of results was undertaken, and there was a slight but definite (6 per cent) improvement in the percentage of patients in the three classes who became bacilli-free, but, as you see, sunlight, except as diffuse daylight, was not a factor.

Of one thing I can speak definitely and without equivocation. All our efforts in the treatment of tuberculosis are, in the absence of specific medication, directed to an improvement in metabolism. Along this line anything that helps is bound to be useful and cause an increase in the percentage of arrests attained. First, we have the old established dietetic-rest-fresh-air treatment; then we add, when we can, a climatic environment, which makes a more or less ideal setting for the application and full utilization of the old method, and, on top of that, exposure of stripped patients to cool, moving air; and now we have a combination of metabolism-aiding factors of the highest utility in the treatment of pulmonary and laryngeal tuberculosis, and, I have no doubt, of equal value in other forms of tuberculosis, and possibly of wide applicability in many nontuberculous disease states.

During the past five years sunlight therapy became so fashionable that I found it impossible to resist it entirely and keep my institution together.

It is a sad commentary on our efforts to be scientific that quite often we find ourselves carried on a current of practice which we may know is opposed to the highest ideals. As a result, I was forced to go back to a combination of the old method, plus sunlight exposure in as small doses as were compatible with the prevailing mode, during the last five years of my work in New Mexico, with the final formation of the opinion that sunlight could have been dispensed with without sacrificing anything in results.

For about twelve years I employed reflected sunlight in all my cases of tuberculous laryngitis, with a definite improvement of 8 per cent in results over other periods, but I found it to be important to shade the patient from the sun during treatment, in all except the most necessary exposure incidental to getting the light into the larynx, and this because these cases usually occur in patients otherwise advanced and often febrile types in which sunlight is detrimental. We all appreciate that sunlight exposure must be avoided in febrile cases and in patients who do not tan, except when intestinal tuberculosis is a complication and one is justified in its use by the gravity of the case and realizing that there is little hope otherwise.

To recapitulate: It is a widely held opinion that sunlight is of little or no use in pulmonary tuberculosis, and this from long experience I know to be correct. But airbaths, let me be equally emphatic, are of great importance, and the time will certainly come when, in favorably located institutions at all times of the year, and in others less favorably situated part of the year, our tuberculosis patients will be stripped of clothing,—all but a breech-cloth as a concession to decency. Patients so exposed do not take cold easily, are not so dependent upon artificial heat, appear better, feel better, eat better and, briefly, recover faster and more surely. The invention of clothing was a not altogether fortunate thing in the history of humanity, and to dispense with it is greatly to the advantage of the tuberculous.

I have said enough, I think, to make it clear that in short-wave light we have an agency of great potency for a little good, perhaps, and also much evil. Just where one begins and the other leaves off, and where they lap over, only time will tell. At this stage, I feel that light is being mostly unscientifically and often carelessly applied, and we are only saved from disastrous reaction in many instances by Nature's ability to protect us from the bad effects by the deposit of pigment. This

careless use of short rays may quite often turn the scale from good to bad results in the treatment of pulmonary tuberculosis especially. We may even have ophthalmias, skin disease, cancer, etc., disturbances of metabolism and internal secretion, and perhaps disorder of the haemopoietic system, caused by light.

These unfortunate results will certainly occur if these actinic lights are sold to the layman to use at his own discretion, in the indiscriminate manner which is being increasingly practised.

Chemical light should be used only under direct medical supervision. At this stage of knowledge even physicians know so little about the application of radiations that they should be very careful indeed until time has better defined the limit of their usefulness.

A movement to replace the glazing of school-windows with a glass that will better transmit actinic rays is perhaps to be commended, although the sensational effect of the sort of glazing reported from England will probably not be wholly substantiated. However, the results, in stimulating the growth and proper development of young children, are sufficiently well-founded, and have a good scientific sanction in research which has demonstrated the necessity for the kind of radiation in young animals, including man. The only question arises from the fact that the best glass so far on the market transmits but 50 per cent of the actinic light, and it is at least possible that in a short time—a few years—we will have at our command panes of quartz or greatly improved glass which will transmit practically all the chemical light contained in sunlight and diffuse daylight. It should also be recalled that in smoky cities very little actinic light gets through during the school months, and not much at any time of the year.

In conclusion, it may be said, and it may be taken at its face value, that if Nature intended us to get very large doses of chemical light she would have put more of these rays in the sunlight, or at least have prevented our tanning to keep them out.

MENTAL ATTITUDE AS A FACTOR IN THE TREATMENT OF TUBERCULOSIS[1]

BLANCHE PETERSON[2]

The prevention of tuberculosis depends largely on an intelligent attitude toward the disease, not only on the part of the public but also on the part of the patient himself. I believe one may go a step further, and say that the most important single factor in the cure of tuberculosis is an intelligent attitude of the patient. On this assumption the mental attitudes of 52 patients toward the disease were studied. The purpose of the study was not to show that the psychology of patients with tuberculosis is peculiar to the disease, but that doctors, nurses and social workers, in close contact with the patients and understanding, as they do, human nature and the psychology of the individual patient, may influence the patient to assume a more intelligent and constructive outlook.

Questionnaires were sent to various physicians[3] who are especially interested in the treatment of tuberculosis. The various attitudes which I had observed in my work with such patients were defined and listed alphabetically as follows:

1: Anxious: concerned as to some future event which disturbs the mind.
2: Ashamed: feeling a lowering in public estimation.
3: Courageous: calm and persistently brave in facing the situation.

[1] Chapter X of a thesis submitted by the writer to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, June, 1927.

[2] Division of Medical Social Service, Mayo Clinic, Rochester, Minnesota.

[3] Letters were sent to Dr. Lawrason Brown, Saranac Lake, New York; Dr. Alexius M. Forster, Cragmor Sanatorium, Colorado Springs, Colorado; Dr. J. A. Britton, Chicago; Dr. John W. Flinn, Pamsetgaaf Sanatorium, Prescott, Arizona; Dr. A. T. Laird, Nopeming Sanatorium, Nopeming, Minnesota; Dr. E. S. Mariette, Glen Lake Sanatorium, Oak Terrace, Minnesota; Dr. Frank Mera, Sunmount Sanatorium, Santa Fe, New Mexico; Dr. S. A. Slater, Southwestern Sanatorium, Worthington, Minnesota; Dr. H. Longstreet Taylor, Pokegama Sanatorium, Pokegama, Minnesota; Dr. R. S. Ferguson, Fort Qu'Appelle, Saskatchewan; Dr. W. D. Beadie, Cannon Falls, Minnesota; Dr. F. M. Pottenger, Monrovia, California; Dr. H. F. Vermillion, Southern Baptist Sanatorium, El Paso, Texas; Dr. F. H. Heise, Trudeau Sanatorium, Trudeau, New York; Dr. J. S. Pritchard, Battle Creek Sanatorium, Battle Creek, Michigan; and Dr. C. E. Harris, Modern Woodmen of America Sanatorium, Woodmen, Colorado.

4: Depressed: hopeless and sad.
5: Discouraged: lacking confidence.
6: Hopeful: desirous of some good accompanied by the belief that it is attainable.
7: Hopeless: without hope.
8: Indifferent: lacking interest in what is presented to the mind.
9: Optimistic: feeling that everything is ordered for the best.
10: Pessimistic: looking on the dark side of things.
11: Reasonable: comprehending the situation and applying common sense.
12: Rebellious: openly defiant.
13: Skeptical: disbelieving, facing argument obstinately.
14: Worried: unduly anxious.
15: Attitude inaccessible: patient did not appear to comprehend the situation or have a definite attitude.

The physicians receiving the questionnaires were asked to re-list these attitudes according to their point of view from the most constructive to the most destructive attitude, and also to answer the following questions:

1. In your opinion how important in his recovery is the patient's attitude toward his disease?
2. Do you consider that the attitude of every patient either aids or interferes with treatment or do you believe that there are certain attitudes which might be classed as neutral attitudes?

Answers which were most interesting as well as highly instructive were received from thirteen of the seventeen in time to be used for this study. It is difficult to classify the opinions of these thirteen medical men, as each had a slightly different view of the subject, but the following general conclusions were arrived at:

1. The patient's attitude has an influence on the effectiveness of treatment.
2. Certain attitudes are constructive or aid in treatment, and certain attitudes are destructive or interfere with treatment; there are also attitudes which do neither and may be classified as neutral.
3. Attitudes are not permanent but are changeable. One attitude may be combined with another and may change in a short time.

Nine of the thirteen physicians answered the questions definitely, and stated that the mental attitude was very important in the patient's recovery. Another stated that the mental attitude of any person aids or interferes with his success in life and, so far as that was true, he believed the mental attitude of the patient with tuberculosis would influ-

ence his recovery. The other three classified the attitudes but made no additional comments. Only one physician felt that attitudes neither aid nor interfere with treatment.

The arrangement of the attitudes, according to the relative value of each and the degree of constructiveness from the most constructive to the most destructive, was made by arriving at an average of the thirteen opinions on each attitude. The following order was arrived at:

1. Courageous
2. Reasonable
3. Hopeful
4. Optimistic
5. Ashamed
6. Anxious
7. Depressed
8. Indifferent
9. Skeptical
10. Attitude inaccessible
11. Discouraged
12. Pessimistic
13. Hopeless
14. Worried
15. Rebellious

Reasonable and courageous attitudes were considered by all as the most highly constructive, and, therefore, the most desirable attitudes to deal with. A reasonable attitude was considered by one the best attitude because it is based neither on temperament nor on physical condition. "Hopeful" and "optimistic" came third and fourth on the list because it appeared that, although these attitudes are constructive, the patients characterized by them are more likely to have "ups and downs" and be difficult to deal with at times. "Ashamed" was considered a neutral attitude in most instances. Some patients may be ashamed to have their friends and neighbors know they have tuberculosis, but with education in regard to the disease this attitude should be corrected so that it would not affect treatment. "Anxious" was considered neutral by two and destructive by the remainder. "Depressed" was considered destructive by all. Indifferent and skeptical attitudes were considered neutral by two and destructive by the remainder. "Inaccessible" was destructive to a certain degree to nine, but to four it was neutral. Discouraged, hopeless, worried, pessimistic and rebellious attitudes were considered, in the main, as highly destructive.

Of what importance is this to the social worker? When an individual first learns that he has tuberculosis, he is probably upset and depressed. Perhaps he knows nothing of the nature of the disease and is sure that it will prove fatal. The patient may be a mother with a young child or a young man just starting out in business, in debt and with no resources. The mental reaction in a normally intelligent person under these circumstances is acute and it is at this time that a great deal of help can be given

the patient. The social worker knows that attitudes are important in the patient's recovery, that certain attitudes are destructive, and certain others constructive. She knows, too, that destructive attitudes can be changed into constructive ones. After the patient has been told that tuberculosis exists, he and his relatives should have a long talk with the physician, who should make it clear that tuberculosis is a curable disease if treated sufficiently early and sufficiently long. In the Mayo Clinic the physician talks to the patient and his relatives, and then sends them to the social worker, who aids the patient in carrying out the doctor's suggestions. The social worker may learn that the patient is depressed and worried because he finds he cannot afford to go to bed for six months or a year, or that, being a mother, she cannot go to a sanatorium because she cannot leave her young child. It is the job of the social worker to find out what obstacles or conditions are distressing the patient and then to assist in removing them. The obstacle may be a social problem or it may be purely the mental attitude. The patient on returning home may have a mental relapse and become despondent. The social worker at the Mayo Clinic, when referring the patient to a local social worker, county nurse or health officer, gives a picture of the patient as she saw him. Much can be done by constant effort of this kind to improve the mental attitude of the patient.

The attitudes of 52 patients when interviewed by the social-service worker have been tabulated.

The scale of attitudes arrived at as the result of the classifications of thirteen physicians applied to the 52 patients may be seen in table 1. The order from the most constructive attitude, which appears first, to the most destructive, which appears last on the list, has been maintained. Only 19 of the 52 patients were found to have a constructive attitude at the beginning of treatment. This should be a challenge to the worker to bring about a change, so that treatment may be more effective. Most of the destructive attitudes may be corrected if remedial efforts are instituted.

Rebelliousness, undue worry and hopelessness are deep-seated, and require a keen insight into the patient's makeup.

It is difficult to say what impression has been made on the 52 patients. The cases have been followed up for six months, either directly or indirectly through a local worker, but in many cases the work has not been completed and reports have not been received. In 19 cases, however, some statement may be made. Judging the patient by overt action, or

by his expression through correspondence, or by the indirect report of another agency, I came to some conclusion regarding the change in attitude. In 7 of the 19 cases the attitude of the patient was constructive to begin with; all of these cases were closed at the end of six months and were considered complete and satisfactory. This means to the worker that the patient went into the sanatorium advised, and those with whom he had been in contact were examined. Four of the 19 patients died. Six others were worried and nervous as to the outcome, and there was improvement in the mental attitude of all of these. Some of the obstacles had been removed and in some instances complete understanding of the disease and association with other patients led to a

TABLE 1

Classification of attitudes of 52 patients according to degree of constructiveness

ATTITUDE	NUMBER OF CASES	DIAGNOSIS JUST ESTABLISHED	DIAGNOSIS KNOWN BEFORE
Reasonable	13	11	2
Hopeful	4	4	
Optimistic	2	2	
Anxious	6	6	
Depressed	2	1	1
Indifferent	2	1	1
Discouraged	3	2	1
Hopeless	1	1	
Worried	6	6	
Rebellious	1	1	
Attitude inaccessible	9	8	1
Unknown; not interviewed	3	2	1
Total	52	51	7

more reasonable attitude. Two cases were closed and no reports were received regarding attitude.

I realize that this study is only an experiment, but I believe that it is a means of showing how unlimited are the opportunities for the worker, be he physician, health officer, county nurse, or social worker, to aid the patient in assuming the right attitude. The most constructive attitude was found to be one that implied courageousness and reasonableness. To be courageous and reasonable one must understand the situation. The patient must know, therefore, something of the nature of the disease, the treatment required for it, and the problems that he must face. He must be calm and persistent in his efforts to effect a cure. Since atti-

tudes change, the worker must also be careful that a constructive attitude does not lapse into a destructive one. In order to prevent this, it is most important that the patient's family as well as the patient himself have an intelligent attitude toward tuberculosis. If the worker can influence a patient and his family to assume such an attitude she has accomplished a most difficult step in the course of treatment. It cannot be done in a short time or by one person, but requires the confidence of the patient and the coöperation of all persons concerned.

THE CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN

IX. THE FRACTIONAL HEAT COAGULATION OF THE PROTEIN OF TUBERCULIN[1,2]

FLORENCE B. SEIBERT

It has always been known that protein in tuberculin withstands considerable heat without evident loss in specific tuberculin activity, and, in fact, the commercial method for manufacturing O.T. involves boiling the bacilli and culture liquid in the open to one-tenth of the original volume.

In an attempt to determine whether the active principle of tuberculin is protein, or, in an endeavor to break off from the protein an infinitesimal quantity of some very potent substance, a study of fractionation by heat is essential. Therefore, the following experiments were undertaken, and, in the main, they support the idea that the active substance is protein.

EXPERIMENTAL

A water-soluble protein fraction of tuberculin was used, the same as in the experiments on crystallization, reported in *Study X* of this series. It had been made from tuberculin supplied by Parke Davis & Co. and the H. K. Mulford Co., for the National Tuberculosis Association, by saturating with ammonium sulphate the raw tuberculin made in a non-protein medium, filtering off the precipitate, dissolving this precipitate in water and dialyzing free of the ammonium sulphate. A small amount of precipitate formed during dialysis, and this was filtered off, and then the solution evaporated *in vacuo* below 50°C. to dryness. This fraction contained all of the specifically active material in the tuberculin.

In experiment 1, 10 gm. of this fraction was triturated in 60 cc. distilled water and a cloudy suspension resulted. This then was heated in a water-bath for one-half hour at 50–52° C.,

[1] From the Department of Pathology and the Otho S. A. Sprague Memorial Institute, University of Chicago.

[2] Aided by a grant to Dr. E. R. Long by the National Tuberculosis Association.

and the coagulum filtered off through hardened filter paper to a clear amber filtrate, then washed with 15 cc. distilled water, and dried *in vacuo* over sulphuric acid at room temperature.

The clear filtrate was then heated to 50°C. for 15 minutes, and there was no more coagulation. After this it was then heated to 70°C. for 20 minutes, and the process repeated in the same way as described above at successively higher temperatures, 80–90°, 97–99°, or boiling over the free flame, and autoclaving at 120°C., a coagulum appearing at each temperature. The final filtrate, after all of these precipitates were removed, was taken to dryness *in vacuo* and is known as the noncoagulable fraction.

Each fraction was then analyzed chemically and tested biologically, and table 1 contains these data.

The nitrogen analyses were run exactly according to the directions given in a previous article (1), and the fractions indicated as follows:

Protein N = total N minus N in trichloroacetic-acid filtrate of a 1 per cent protein solution.

Proteose N = N in trichloroacetic-acid filtrate minus N in phosphotungstic-acid filtrate.

Residual N = N in phosphotungstic-acid filtrate.

NH_3 and amide N = N distilled over from saturated NaOH solution under atmospheric pressure.

From table 1 it will be seen that over 50 per cent of the actual weight of the protein is coagulated at 50° and 70°, and above that temperature only 10–11 per cent more can be coagulated, even by autoclaving at 120°C. and 15 lbs. pressure for one-half hour. The other 34 per cent is truly noncoagulable at the pH of 5.4–5.6, at which the coagulation was carried out. Of this noncoagulable fraction, 71 per cent of the bulk, or 45.3 per cent of its nitrogen, did not dialyze through a fish-bladder membrane. In this nondialyzable fraction there was less than 5 per cent total nitrogen, and half of this was whole-protein nitrogen. Presumably there was much carbohydrate, since the Molisch reaction was marked and the nitrogen content low.

All six fractions in 0.1 mgm. doses produced moderate tuberculin skin reactions, with a few maximum (5+) reactions scattered throughout. It would seem, therefore, that the specific activity is not directly associated with any one fraction more than any other, but rather that it is present whenever the tuberculin protein is present, even in the noncoagulable fraction.

The fact that various fractions can be removed at different temperatures may not necessarily mean that there are correspondingly different proteins, but merely that the same protein exists in various stages of denaturation (see discussion in *Study X*) and that these varying stages

TABLE 1

FRACTIONS	YIELD FROM 10 GM.	PER CENT OF YIELD	PROTEIN TESTS					NITROGEN ANALYSIS					SKIN TESTS (WITH 0.1 MGM.)		MINIMAL LETHAL DOSE IN MILLIGRAMS
									Per cent of total as						
			Biuret	Millons	Vanillin	Ninhydrin	Molisch test	Per cent total	Whole protein	Proteose	Residual	NH_3 and amide	Normal guinea pigs	Tuberculous guinea pigs	
Original	10.0		+	+	++	+	+++	10.82	78.7	8.6	12.8	13.4	−, −	4–5+, 5+, 5+	1 mgm. {3 died, 3 lived}; 2 mgm. {5 died, 1 lived}
50°	2.25	27.6						10.95	87.1	4.2	8.7	8.5	−	2+, 3+, 3+, 5+	3 mgm.
70°	2.16	26.5	+	++	+		Trace	11.93	91.4	3.2	5.4	10.1	−, −	1+, 3+, 4+	1 mgm. {1 died, 2 lived}; 2 mgm. (1 died)
80–90°	0.70	8.6	+					12.34	95.6	0.9	3.4	11.6	1+, 2+, 1+	2+, 3+, 3+	2 mgm.
97–99°	0.097	1.2						10.28	81.3	11.3	7.4	11.9	1+, 2–3+	5+, 5+	3 mgm.
Autoclaved at 120°	0.092	1.12						10.82	88.3	4.7	6.9	11.2	tr, 2+	2–3+, 4+	3 mgm.
Noncoagulable	2.85	34.02	+	++	++++	+	++++	7.08	29.5	61.6	8.9	20.8	−, −,	2+, 2–3+, 5+	0.5 mgm.
Total recovery	8.15	81.5													
Residue on dialysis of 1.2 gm. noncoagulable	0.81	71.05	+		+		+++++	4.75	50.3	25.3	24.4	9.9	2+	3+, 3+	4 mgm. (lived)
Diffusate	0.33	28.9	−		Faint		Faint	11.06	0.0	23.7	76.8	28.8	3+	2–3+, 4+	4 mgm. (lived)

are indicated by a slight change in coagulation temperature, just as there are slight changes in solubility of the protein accompanied by changes in biological activity, as will be shown later.

Based upon the lethal test, the noncoagulable fraction seemed to be the most potent, for only 0.5 mgm. of it was required to kill a tuberculous guinea pig, whereas 1 to 3 mgm. of the other fractions were required.

Since it was no more active than the other fractions, as indicated by the tuberculin skin reaction, it may be that the increased toxicity, as regis-

TABLE 2

FRACTION	GRAMS YIELD	TOTAL N	PROTEIN N	PROTEOSE N	NH_3 AND AMIDE N	RESIDUE NITROGEN
	grams	*grams*	*grams*	*grams*	*grams*	*grams*
Original	10	1.082	0.852	0.0930	0.1450	0.1390
50° fraction	2.25	0.246	0.215	0.0103	0.0209	0.0214
70° fraction	2.16	0.257	0.235	0.0084	0.0261	0.0138
80–90° fraction	0.70	0.086	0.083	0.0008	0.0100	0.0029
97–99° fraction	0.097	0.010	0.008	0.0011	0.0012	0.0007
Autoclaved at 120°	0.092	0.010	0.009	0.0005	0.0011	0.0007
Noncoagulable	2.85	0.201	0.059	0.124	0.0418	0.0179
Total added from fractions	8.149	0.810	0.609	0.145	0.1011	0.0574
				(*gain*)		
Loss from original	1.85	0.272	0.243	+0.052	0.043	0.081
Percent of loss	18.5%	25.1%	28.5%	+56.00%	29.6%	58.2%
On dialysis of 2.85 gm. of noncoagulable fraction						
	grams					
Residue	1.923	0.092	0.046	0.023	0.009	0.022
Diffusate	0.784	0.087	0.000	0.021	0.025	0.066
Sum	2.707	0.179	0.046	0.044	0.034	0.088
Losses during dialysis	0.143	0.022	0.014	0.080	0.008	+0.070

tered by the lethal test, is largely a nonspecific effect, possibly due to an injurious proteose. That this is very probably true is seen in the next series of experiments, in which it was found that the lethal dose of the noncoagulable fraction for normal guinea pigs was smaller than the lethal dose of other fractions. In support of the idea that the primarily toxic factor may be a proteose, the table shows that the noncoagulable fraction contains far more proteose than the other fractions. This is brought out more clearly when the analyses are recorded as actual grams of

various types of nitrogen in various fractions (see table 2). Of course, slight mechanical losses must be considered, which prevent perfect agreement between the nitrogen figures in the original 10 gm. used and those obtained by addition of the various fractions.

Comparing the amounts of nitrogen in the original 10 gm. of protein with the amounts of nitrogen in the sum of its fractions, it will be seen that there is considerable loss during heating in the total nitrogen, and furthermore that this loss is chiefly in the whole protein nitrogen, while there is a slight total gain in proteose nitrogen, which is therefore a possible indication of hydrolysis by the heating. Much of the nitrogen, however, must have been completely lost as free NH_3.

It was surprising to find that no true tuberculin skin reaction, but only a nonspecific response, which was about equal in tuberculous and normal guinea pigs, was produced by both diffusate and residue after dialysis of the noncoagulable fraction through a fish-skin membrane. The specifically active material was lost during dialysis. Since the largest loss during dialysis occurred in the proteose fraction, there is a temptation to conclude that the active material was this proteose which was lost. But such a conclusion would be hasty, especially in the light of work reported in the following paper. It seems more probable that the loss in activity is due to a denaturization of the protein during dialysis and that the losses in proteose may be just accidentally parallel. Another possibility is that the specifically active protein was adsorbed by the dialysis membrane and therefore removed from solution, just as was shown by Dorset (2) to occur when filtering small quantities of tuberculin through the Berkefeld candle.

Further study of the noncoagulable fraction was made in a second experiment.

Of the same water-soluble fraction as used in the last experiment, 14.7 gm. was triturated in 200 cc. distilled water and autoclaved for one hour at 15 lbs. pressure and 120°C. The coagulum was suspended again in distilled water, autoclaved for 15 minutes, filtered, and washed. The filtrates were mixed and then evaporated to dryness *in vacuo*. This is the noncoagulable fraction (wt., 4.67 gm.).

The precipitate was washed with 95 per cent alcohol until the wash came colorless and then with ether several times. The weight of the dried precipitate was 7.86 gm. This is the heat-coagulable fraction.

The alcohol and ether washes also were dried, and weighed 0.07 gm.

The results of tests with these products are contained in table 3.

In this experiment, as in the former one, about 50 per cent of the total nitrogen in the noncoagulable fraction after dialysis is whole-protein

TABLE 3

FRACTIONS	AMOUNT	NITROGEN ANALYSES				BIOLOGICAL TESTS IN GUINEA PIGS			
			Per cent of total N as			Skin tests		Lethal tests	
		Total N	Protein N	Proteose N	Residual N	Normal guinea pigs	Tuberculous guinea pigs	Normal guinea pigs	Tuberculous guinea pigs
	grams	*per cent*							
Original	14.7	10.82	78.77	8.6	12.8	−, −	4–5+, 5+, 5+	100 mgm. {2 died, 4 sick, 1 recovered 150 mgm.; died	1 mgm. {3 died, 3 lived 2 mgm. {5 died, 1 lived
Heat-coagulable	7.86	13.88				−, tr, −	2+, 3+, 3+ 3–4+, 4+	150 mgm.; no reaction 150 mgm.; no reaction	1 mgm.; 1 lived 2 mgm.; 1 died 5 mgm.; 1 died
Noncoagulable	4.67	7.61	32.98	34.03	32.98	−, 1+, 1+	2+, 2+, 3+, 3+ 3–4+, 3–4+, 5+	150 mgm.; sick, recovered 150 mgm.; died	1 mgm.; 1 died 1 mgm.; 1 died
Noncoagulable residue on dialysis (2.5 gm. used), (1.72 gm. obtained)	3.21*	6.25	51.04	32.00	17.00	tr, 1+	4+, 4–5+	100 mgm.; recovered 150 mgm.; died	1 mgm.; 1 lived 2 mgm.; 1 died
Noncoagulable diffusate (2.5 gm. used), (0.65 gm. obtained)	1.21*					−, 1+	2–3+, 3+	50 mgm.; no reaction 150 mgm.; recovered	1 mgm.; 1 lived 2 mgm.; 1 died in 3 days

* These amounts are calculated on the basis of the entire 4.67 gm. noncoagulable fraction.

nitrogen, and another very large percentage of the total nitrogen exists as proteose nitrogen. This noncoagulable fraction gives a specific tuberculin skin reaction, presumably due to the whole protein still present, and this specific reaction is no greater than was produced by the heat-coagulable fraction. The primary toxicity, however, for normal as well as tuberculous animals, has been increased over that for the heat-coagulable fraction, since 150 mgm., injected intraperitoneally into normal guinea pigs, caused far worse symptoms and even death than the same amount of the heat-coagulable fraction, which was tolerated by normal animals practically without any symptoms. This increase may possibly be accounted for, as in the former experiment, by the increase in proteose present, as shown by chemical analyses.

A detailed study is being made of this primary toxicity of the tuberculin protein for normal animals, and its relationship to the specificity of the reaction, and will be reported in detail in a latter publication. It seems possible that further purification of the tuberculin protein may help to eliminate this primary toxic factor present, and thus lead to more reliable results in specific immunological reactions.

CONCLUSIONS

1. A protein-free fraction giving the specific tuberculin reaction could not be separated from the whole protein of tuberculin by fractional heat coagulation.

2. Fractions coagulated at 50°, 70°, 80–90°, 97–99° (boiling), 120° (autoclaving), and even the final noncoagulable fraction, which also definitely contained some whole protein, all gave equally marked tuberculin skin reactions, indicating that the specific biological activity is not due to any particular fraction but rather accompanies all fractions where the tuberculin protein is present.

3. All fractions may therefore be derivatives of the same protein in varying stages of chemical change. Experiments to be reported in the following paper (*Study X*) indicate that these variations in coagulability are analagous to variations in solubility of different fractions of the same protein.

4. The noncoagulable fraction has more primary toxicity than the coagulable fractions, as indicated by the lethal test, for normal as well as for tuberculous animals, although it gives no more marked specific skin reaction in tuberculous animals. We must, therefore, in considering the tuberculin reaction, recognize a certain primary toxicity of tuberculin

in addition to its well known capacity to elicit the specific tuberculin reaction in infected animals.[3]

I wish to express my gratitude to Dr. E. R. Long through whom this work has been made possible.

REFERENCES

(1) SEIBERT, F. B.: J. Biol. Chem., 1926, lxx, 265.
(2) DORSET, M.: J. Amer. Vet. Med. Assoc., 1926, lxx.
(3) DORSET, M., HENLEY, R. R., AND MOSKEY, H. E.: Ibid., 1927, lxxi, 487.

[3] When this work was ready for press there came to my attention an article by Dorset, Henley and Moskey (3), some of the results of which are supported by this report.

THE CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN

X. THE ISOLATION IN CRYSTALLINE FORM AND IDENTIFICATION OF THE ACTIVE PRINCIPLE OF TUBERCULIN[1,2]

FLORENCE B. SEIBERT

Many investigators, beginning with Koch himself (1), have thought that the active constituent of tuberculin, which is responsible for the specific skin reaction in tuberculous subjects, is protein. Most of the work heretofore reported from our laboratory has confirmed this view. For example, the active substance does not dialyze through membranes which keep back proteins (2). It is precipitated only by those reagents which precipitate proteins, and quantitatively only by those which precipitate proteins quantitatively (3). This evidence, of course, does not bar the argument that the active principle may be attached to protein in some loose combination, and, therefore is simply found when protein is present. Evidence, however, which is almost conclusive, that the active substance is whole protein, has already been presented (4). It was found, for example, that when the whole water-soluble active fraction from tuberculin, which had been shown chemically to contain both whole protein and proteose, was treated with the proteolytic enzymes, pepsin and trypsin, at the proper reaction, only the whole protein was materially attacked and simultaneously the specific biological activity of the preparation disappeared. The proteose in the mixture, on the other hand, was then separately attacked by erepsin, but this chemical disruption was not followed by loss in biological activity. The activity, therefore, must have been associated only with whole protein. More final, however, than any of this evidence, would be results obtained with a product which would satisfy the criterion of purity from a chemical standpoint. Such evidence, in fact, is necessary to clinch the problem, and therefore much further effort was expended toward this end.

[1] From the Department of Pathology and the Otho S. A. Sprague Memorial Institute, University of Chicago.

[2] Aided by a grant to Dr. E. R. Long by the National Tuberculosis Association.

Every attempt to separate from the protein in tuberculin an active substance had failed. Fractional salting out with ammonium sulphate gave no one fraction more potent than any other fraction. Fractional coagulation by heat did not give any evidence that the active substance is other than protein or that it is contained in a special fraction of the protein. (For these data see the previous paper, *Study IX.*) Continuous extraction for twenty-four hours each with ether, methyl alcohol and ethyl alcohol did not remove from the water-soluble protein-powder fraction any activity, for the minimal lethal dose, 2 mgm., was not changed by this treatment of the original material.

Throughout all this work it became evident that the water-soluble protein in tuberculin was quite similar in many of its properties to ovalbumin, and the possibility of crystallizing it presented itself, in spite of the fact that no crystalline protein of bacterial origin has been reported in the literature. Crystallization is one of our first and most important criteria of purification of any compound and seemed therefore worth much effort.

A protein, in order to crystallize, must be in as nearly the natural state as possible, and therefore it cannot be hoped to obtain crystals from any protein mass which has received sufficiently drastic treatment to cause the slightest denaturization. This principle has been adhered to throughout this work and, when it was found that complete saturation with ammonium sulphate would remove the active substance from tuberculin completely with the least evident change, this was the method (3) adopted for making the first crude separation for all future lots of material. Parke, Davis and Company and the H. K. Mulford Company have generously coöperated with the National Tuberculosis Association in supplying large quantities of material made by this method. The tuberculin used in this study and all of the studies so far reported by the author has been made upon the protein-free synthetic medium recommended by Long (5).

A note here as to the yields of protein in such tuberculin is not out of place. Table 1 shows that from 0.13 to 0.74 gm. of the water-soluble protein was obtained per litre of tuberculin by saturating the latter with ammonium sulphate, dialyzing free from this salt, filtering and then drying *in vacuo* at such a low temperature as to cause no coagulation of the protein (below 50°C.)

Starting with 0.5 to 1 gm. at a time of these water-soluble protein fractions, attempts were made to crystallize from them a protein, by

Hopkins's method for crystallizing ovalbumin (6). Eleven different trials with five different lots of material proved successful and burrs or bundles of crystalline needles were obtained, usually mixed with amorphous particles. Figure 1 shows the mixture and its likeness to ovalbumin crystals.

METHODS AND TECHNIQUE

Experiment 1: One gram of lot *K* of water-soluble fraction was dissolved in 10 cc. of distilled water and to it was added 10 cc. of saturated ammonium sulphate. This precipitate was filtered off the next morning, and to the filtrate was added two drops 10 per cent acetic acid to a slight permanent precipitate, and then 0.17 cc. more added to a heavy white precipitate, which was amorphous. The precipitate was filtered off, and to the filtrate saturated ammonium sulphate was added until a permanent precipitate was obtained, which also was amorphous. This precipitate was filtered off and redissolved in a small amount of distilled water, and to the filtrate was added saturated ammonium sulphate. On the next morning this precipitate contained many scant burrs and single needles mixed with much amorphous precipitate. Figure 1 represents this preparation. On re-solution and precipitation very few needles were obtained, and the precipitate was dissolved in water, dialyzed, and then dried *in vacuo*. Skin tests with 0.1 mgm. doses in tuberculous guinea pigs were negative. As can be concluded from experiments reported later in the paper, the biological activity may have been lost during dialysis.

TABLE 1

LOT OF TUBERCULIN	LITRES OF TUBERCULIN SATURATED	YIELD OF WATER-SOLUBLE PROTEIN	YIELD OF OTHER PROTEINS	YIELD PER LITRE OF WATER-SOLUBLE PROTEIN	YIELD PER LITRE OF TOTAL PROTEIN	AGE OF CULTURE
		gm.	*gm.*	*gm.*	*gm.*	*weeks*
H	30	15.2	0.9	0.50	0.54	8
I	25	6.8	0.9	0.27	0.31	7
K	49	9.4	1.2	0.19	0.22	8
L	48	13.4	8.3	0.28	0.45	8
Q	27	3.4		0.13		7
(a)	40	9.2	2.7	0.23	0.30	8
(b)	288	126.1	0.9	0.44	0.44	5
	2.7	0.5		0.18		6
	1.35	1.0		0.74		12

Experiment 2 (7): One gram of lot *L* of water-soluble fraction was dissolved in 12 cc. of distilled water and then treated by the same technique as above

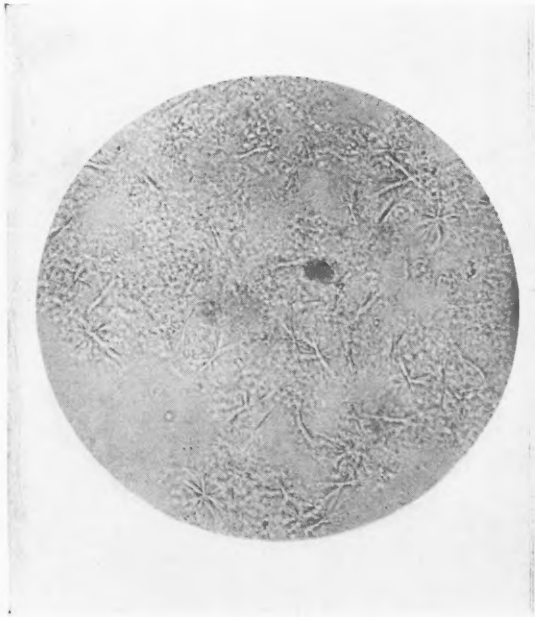


FIG. 1. SUBSTANCE OBTAINED IN EXPERIMENT 1
For source and preparation see p. 404 of text

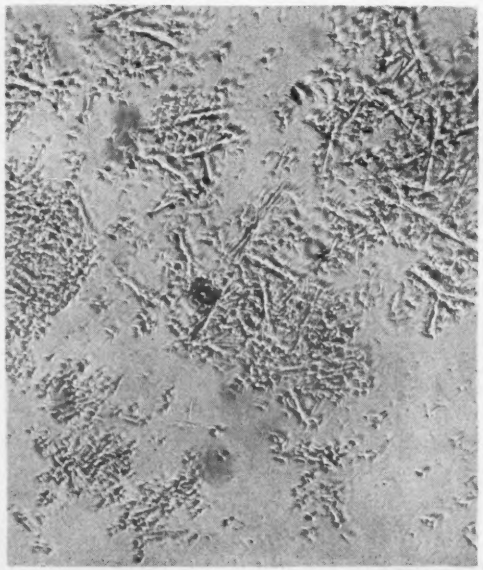


FIG. 2. SUBSTANCE OBTAINED IN EXPERIMENT 2
For source and preparation see p. 404 of text

FIG. 3. SUBSTANCE OBTAINED IN EXPERIMENT 6
For source and preparation see p. 406 of text

described, when almost pure needles were obtained. About half of this crystalline precipitate (figure 2) was filtered off, and dissolved in 3 cc. of distilled water and filtered again. The filtrate gave a pink biuret test, was heat-coagulable, and produced skin reactions (4+, 5+, 5+) in tuberculous guinea pigs but negative reactions in nontuberculous normal animals.

Experiments 3 and 4: Crystals were obtained from lots *I* and *L* of the water-soluble fraction in the same way, but they also were mixed with much amorphous material.

Experiment 5: 2,230 cc. of clear dialyzed tuberculin made from nonprotein medium was saturated with solid ammonium sulphate, and the next morning the precipitate was filtered off. It was then dialyzed, filtered, and concentrated *in vacuo* at 40–50°C. to 20 cc. To this was added an equal volume of saturated ammonium sulphate, and from here the process was carried forward as described in experiment 1. Finally numerous crystals were obtained.

Experiment 6 (8)*:* One gram of lot *L* of water-soluble fraction was dissolved in 12.5 cc. of distilled water, and 12.5 cc. of saturated ammonium sulphate added. The precipitate was let stand one to two hours and then filtered. It was then washed with 5 cc. of half-saturated ammonium sulphate, and this wash was allowed to stand for a few hours, during which time a flocculent precipitate appeared, which microscopically was nothing but solid crystals (see figure 3). Individual drops of the suspension were tested with drops of 0.6, 0.5, 0.45 and 0.4 saturated ammonium sulphate microscopically, and no evident solution occurred, nor precipitation of the amorphous particles. Therefore, the crystals were centrifugated off. (In other cases the crystals could not be separated by centrifugation, but instead remained suspended in solution as if of the same specific gravity as the ammonium sulphate.) They were then washed with 40 cc. of half-saturated ammonium sulphate and a second time with 20 cc. more, in which they were allowed to stand over night, and then centrifugated off. The amount of precipitate was very small, but it was dissolved in 3 cc. of distilled water, and upon 0.5-cc. portions of this solution the following tests were secured: a very faint but positive biuret, a positive Molisch, a positive histidine, a positive cystine sulphur, and a negative Millon's, glyoxylic and vanillin. The crystals stained blue with methylene-blue and were heat-coagulable. Negative skin tests resulted from the injection of 0.1 cc. of the aqueous solution into three tuberculous guinea pigs. The negative results in this case were very puzzling and prompted much further work.

Experiment 7: Again crystals were obtained from 0.25 gm. of lot *L*.

Experiments 8, 9, 10 and 11: In four experiments crystals were obtained from 0.5, 1.0, 2.0 and 1.0 gm. lots of (*b*) respectively, but even by varying the concentration of acetic acid or the amount of ammonium sulphate added absolutely pure crystals were not obtained. The crystalline precipitates were filtered off, washed with three-fourths-saturated ammonium sulphate, and dissolved in 1 cc. of water, filtered, and then tested intracutaneously on guinea pigs in 0.1-cc. doses. Three tuberculous guinea pigs gave a 5+ skin reaction, which consisted of an extensive area of induration, a large necrotic centre, and a superficial scab reaction due to the high concentration of ammonium sulphate. Two normal animals showed only the superficial scab reaction without induration or inflammation. Of two tuberculous guinea pigs given the testicular test, one gave no reaction and one showed extreme atrophy of the germinal cells; while two normal animals gave no reaction.

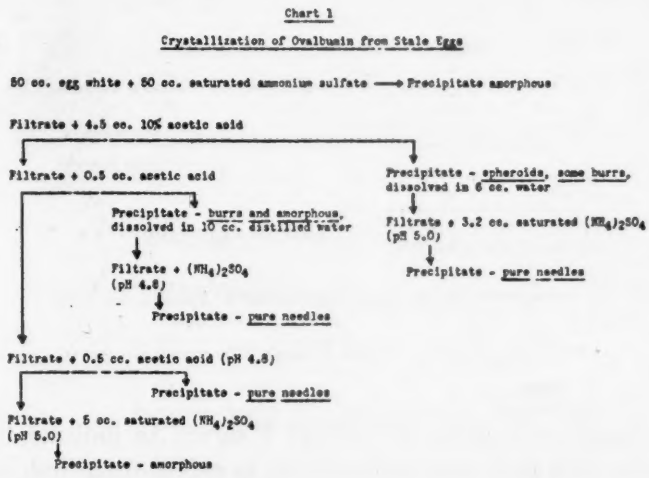


Chart 1
Crystallization of Ovalbumin from Stale Eggs
50 cc. egg white + 50 cc. saturated ammonium sulfate → Precipitate amorphous
Filtrate + 4.5 cc. 10% acetic acid
Filtrate + 0.5 cc. acetic acid
Precipitate - spheroids, some burrs, dissolved in 6 cc. water
Precipitate - burrs and amorphous, dissolved in 10 cc. distilled water
Filtrate + 3.2 cc. saturated $(NH_4)_2SO_4$ (pH 5.0)
Filtrate + $(NH_4)_2SO_4$ (pH 4.8)
Precipitate - pure needles
Precipitate - pure needles
Filtrate + 0.5 cc. acetic acid (pH 4.8)
Precipitate - pure needles
Filtrate + 5 cc. saturated $(NH_4)_2SO_4$ (pH 5.0)
Precipitate - amorphous

There is a very strong suggestion in these experiments that the crystals may be the active principle, but only once, as if by chance, were absolutely pure needles obtained. It could, therefore, never be stated definitely whether the tuberculin activity was due to the crystals themselves or to the amorphous particles always found present along with the crystals. There was the possibility, however, as with ovalbumin, that the amorphous particles were precursors of needles or were needles whose formation had been retarded. One of the chief difficulties seemed to be that sufficient original material had not been used to warrant recrystallization and further purification.

At this point, I wish to express my gratitude to Drs. Mendel, Osborne and Vickery, for their suggestions and encouragement, and particularly

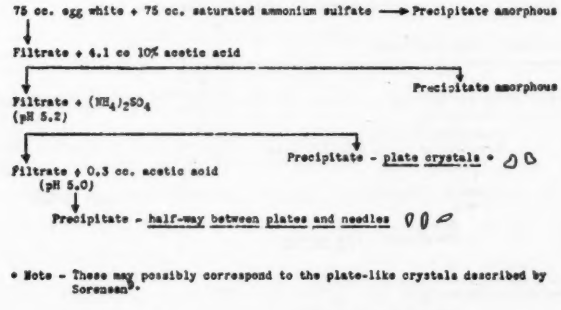
to Professor Mendel, for the use of his laboratory at Yale University where the following two experments (see charts 1, 2 and 3) were carried out.

The crystallzation of ovalbumin from strictly fresh eggs requires considerable care and practice, as is well known, and it was soon recognized that the crystallization of this protein from tuberculin was much more difficult. Since the literature emphasizes the exceptionally great difficulty of making crystals from stale eggs, it was deemed worth some effort to work up technique on such material. Consequently, the whites of a dozen low-grade store eggs were treated by Hopkins's method (6), and pure needles were obtained, but only after repeated attempts were made on succeeding filtrates.

The outlines of these trials are given in chart 2.

Chart 2

Crystallization of Ovalbumin from Stale Eggs


75 cc. egg white + 75 cc. saturated ammonium sulfate
Precipitate amorphous
Filtrate + 4.1 cc 10% acetic acid
Precipitate amorphous
Filtrate + $(NH_4)_2SO_4$
(pH 5.2)
Precipitate - plate crystals *
Filtrate + 0.3 cc. acetic acid
(pH 5.0)
Precipitate - half-way between plates and needles

* Note - These may possibly correspond to the plate-like crystals described by Sorensen[9].

These experiments depicted in chart 2 served to indicate that it is possible to obtain pure crystals from stale as well as from fresh eggs, provided the hydrogen-ion concentration of the solution is controlled and the first amorphous precipitates are discarded or worked over.

Such a procedure and even more extensive purification were needed to obtain pure crystals from the tuberculin protein. Chart 3 shows an experiment involving the use of 20 gm. of the water-soluble tuberculin protein (lot *b*) which would represent the protein from about 50 litres of tuberculin.

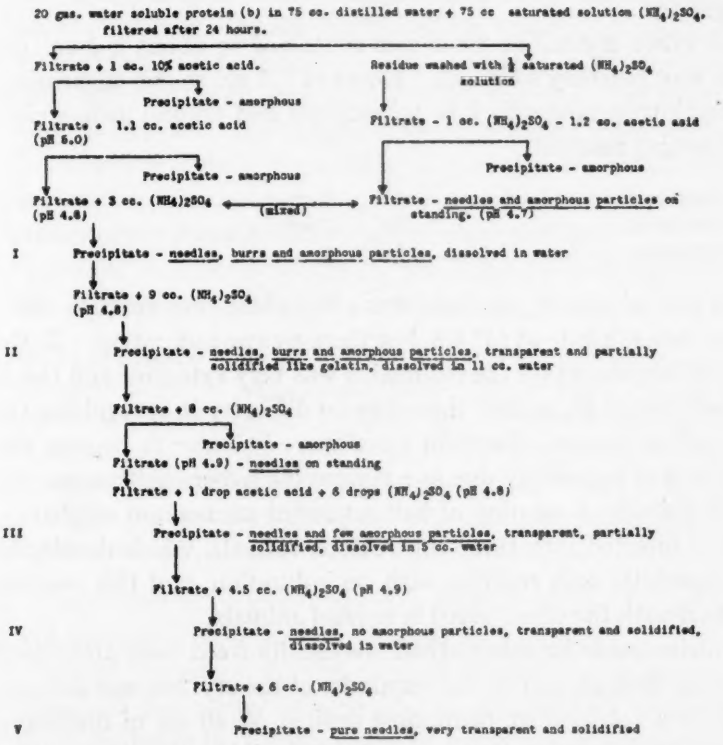
In the experiment recorded in chart 3 only 10 per cent acetic acid and a saturated solution of ammonium sulphate were used, and every filtration was carried out through hardened filter paper.

The optimum crystallization point appears to be at a hydrogen-ion concentration of pH 4.8. The final crystalline product in this experi-

ment, therefore, had been dissolved five times in distilled water and filtered each time through hardened filter paper to a crystal-clear solution, which was then recrystallized again. This final protein resembled egg albumin, therefore, in that it crystallized into needles by the same method and at approximately the same hydrogen-ion concentration, pH 4.8. It differed in that the needles were much finer, more graceful

Chart 3

Crystallization of Tuberculin Protein


20 gms. water soluble protein (b) in 75 cc. distilled water + 75 cc saturated solution $(NH_4)_2SO_4$, filtered after 24 hours.
Filtrate + 1 cc. 10% acetic acid.
Precipitate - amorphous
Filtrate + 1.1 cc. acetic acid (pH 5.0)
Precipitate - amorphous
Filtrate + 3 cc. $(NH_4)_2SO_4$ (pH 4.8)
(mixed)
Residue washed with ½ saturated $(NH_4)_2SO_4$ solution
Filtrate - 1 cc. $(NH_4)_2SO_4$ - 1.2 cc. acetic acid
Precipitate - amorphous
Filtrate - needles and amorphous particles on standing. (pH 4.7)
I
Precipitate - needles, burrs and amorphous particles, dissolved in water
Filtrate + 9 cc. $(NH_4)_2SO_4$ (pH 4.8)
II
Precipitate - needles, burrs and amorphous particles, transparent and partially solidified like gelatin, dissolved in 11 cc. water
Filtrate + 8 cc. $(NH_4)_2SO_4$
Precipitate - amorphous
Filtrate (pH 4.9) - needles on standing
Filtrate + 1 drop acetic acid + 6 drops $(NH_4)_2SO_4$ (pH 4.8)
III
Precipitate - needles and few amorphous particles, transparent, partially solidified, dissolved in 5 cc. water
Filtrate + 4.5 cc. $(NH_4)_2SO_4$ (pH 4.9)
IV
Precipitate - needles, no amorphous particles, transparent and solidified, dissolved in water
Filtrate + 6 cc. $(NH_4)_2SO_4$
V
Precipitate - pure needles, very transparent and solidified

and far more transparent, and also that they remained suspended in the solution, indicating that their specific gravity was less or no greater than one-half-saturated ammonium sulphate. The mass of needles did not appear crystalline to the naked eye, but rather like partially solidified gelatine. The proof that the crystals are protein lies in the facts that they take a definite blue stain with methylene blue, give the biuret, Millon's and vanillin tests, and are heat-coagulable.

These crystals were about as pure as any so far obtained, and under the ordinary microscope appeared to be free from amorphous particles. Some of them, stained with methylene blue, were sealed on a slide to prevent evaporation, and after about a month quite evident amorphous particles could be seen mixed with the crystals. (Reference will be made to this fact later.) One of the most striking facts concerning the protein is the very small quantity obtained from relatively large quantities of tuberculin; so small, indeed, that even in this case it did not seem practical to try to determine the amount of protein present by means of the nitrogen test.

The whole crystalline mass was contained in about a 5-cc. volume, which was partially solidified. Doses of 0.1 cc. of this suspension were injected intracutaneously into tuberculous and normal guinea pigs with the following results:

Tuberculous	4+	Normal	1–2+
Tuberculous	5+	Normal	1+
Tuberculous	5+		

In the normal guinea pigs there was a superficial scab reaction due to the ammonium sulphate at pH 4.8, but there was no induration. In the case of the tuberculous pigs the induration was very extensive and the area of necrosis was large, so that there was no difficulty in recognizing these as true and maximum tuberculin reactions. In order to be sure that the reaction was not simply due to a nonspecific hypersensitiveness of tuberculous animals, a solution of half-saturated ammonium sulphate at pH 4.8 was injected into three tuberculous animals, which developed only the superficial scab reaction with no induration, and this reaction was identical with the effect noted in normal animals.

Proteins made by this method are usually freed from ammonium sulphate by dialysis, and so the remainder of the crystals was dialyzed over night in a fish-bladder membrane against 30–40 cc. of distilled water. On the following day there was a considerable quantity of white flocculent masses in the residue within the sac, and when this suspension was injected into a tuberculous guinea pig it gave a negative reaction contrary to the undialyzed crystals (tuberculous 1+; normal, trace). The diffusate also gave practically no reaction (tuberculous, 1+, trace, trace; normal, trace, trace).

The residue then was taken down to dryness *in vacuo* at 37°–40°C., when it weighed 70 mgm. Two milligrams of the original (lot *b*) water-

soluble protein usually constituted a lethal dose for 500-gm. guinea pigs. Inasmuch as this residue was not completely free from ammonium sulphate, 8 mgm. were injected intraperitoneally. No effect was produced in a tuberculous guinea pig.

Therefore, these experiments suggest that the crystalline protein has tuberculin activity, but on dialysis some of it becomes denaturized, when it loses its biological activity at the same time that it loses its solubility in water. There is the other possibility, that the active substance is absorbed by the dialysis-membrane, since it is found in neither diffusate nor residue. This same strange loss in activity was recorded in a former paper on fractional heat-coagulation (10), when the noncoagulable residue, which had previously given a tuberculin reaction, completely lost its activity on dialysis. Both of these results occurred when very small quantities of active material were dialyzed, and they may be due to the same phenomenon that caused loss in activity when Dorset (11) filtered small quantities of tuberculin through Berkefeld candles.

That a similar loss does occur during the dialysis of large quantities of tuberculin is illustrated by the following data:

A 288-litre lot of tuberculin was saturated with ammonium sulphate, and from it was obtained 126 gm. of water-soluble protein (*b*), of which 2 mgm. was a lethal dose for 500-gm. tuberculous guinea pigs. A 250-cc. portion of the original tuberculin was dialyzed through parchment for three days, so that the nitrogen content of the tuberculin could be determined. The volume had increased to 280 cc., so that 1 cc. of original tuberculin represented 1.18 cc. of dialyzed tuberculin.

Table 2 will show the losses in potency that occurred during dialysis and during the final process of taking the protein to dryness.

It can be seen, therefore, that 50 per cent of the lethal doses was lost by mere dialysis and sufficient previous experiments (2) have shown that it is not probable that this amount of active substance could have dialyzed through the membrane. It is more probable that biological denaturization of the protein occurred during dialysis. A further loss of about 7.8 per cent in lethal doses occurred as the dialyzed material was being taken down to dryness. Some of this loss naturally was actual loss of material due to the difficult filtrations, etc.; nevertheless, the experiment shows that there is a disappearance of much of the activity during dialysis. This method of purification of the crystals, namely, dialysis by the usual method, must therefore be avoided in future experiments.

It seemed advisable, however, to determine what became of all of the active material in the 20 gm. of water-soluble protein used for the crystallization. Therefore, the fractions, "before" and "after" the separation of the crystalline fractions, were saved and tested.

It will be remembered that the method calls for the addition of an equal volume of saturated ammonium-sulphate solution to the water solution of the protein. This precipitate, resulting from half-saturation of the solution, is then filtered off, and attempts are made to obtain crystals from the filtrate by adjusting its hydrogen-ion concentration, as noted in chart 3. The half-saturation precipitate, therefore, is called the fraction "before" crystallization. All of the filtrates, which remain after the crystals are removed and from which no more crystals can be formed, are mixed, and these are then completely saturated with ammonium sulphate, and this precipitate is known as the fraction "after" crystallization.

TABLE 2

	VOLUME	LETHAL DOSE IN TUBERCULOUS GUINEA PIG	TOTAL LETHAL DOSES	LOSS
Original undialyzed tuberculin	288 litres	2 cc.	144,000	
				per cent
Dialyzed tuberculin (250 cc. original tuberculin used for test)		4.8 cc. = 4.0 cc. of original tuberculin	72,000	50
	gm.			
Tuberculin water-soluble powder (2 lots)	116.8	(2 mgm.)	(58,410)	
	9.3	(4 mgm.)	(2,300)	7.8
	126.1		60,710	

The former fraction, or precipitate following half-saturation, was dissolved in water, a residue remaining on filtration. The filtrate was again half-saturated and this process was repeated five times, after which the final precipitate was dissolved in water, dialyzed free from ammonium sulphate, and taken down to dryness (weight 2.36 gm.). At each solution and filtration an insoluble residue remained (total, 1.68 gm.), showing that there is a continual shift in solubility of the protein during manipulation. This final purified half-saturated fraction, when tested on tuberculous guinea pigs, gave the following results:

Tuberculous.....5+ Tuberculous..died in tuberculin shock
Tuberculous.....4+ Normal.....negative

Similarly, the fraction "after" the crystals were removed, was completely saturated with ammonium sulphate five times, with solution in water and filtration after each precipitation, and then finally dialyzed free from ammonium sulphate and dried *in vacuo*. The final weight was 1.355 gm., and there was only a small residue after each filtration. This final product produced in tuberculous animals the following reactions:

Tuberculous	5+	Normal	negative
Tuberculous	5+		

Therefore, while the crystalline fraction seems to be potent from a tuberculin standpoint, it is no more potent than other protein fractions which do not crystallize. The interpretation of all these facts is found in the discussion following the next experiment.

In order to be entirely satisfied on the point that the crystals are active, another experiment was undertaken, in which 50 gm. of the water-soluble fraction, tuberculin lot (*b*), corresponding to 113.6 litres of tuberculin, were used. (See chart 4.)

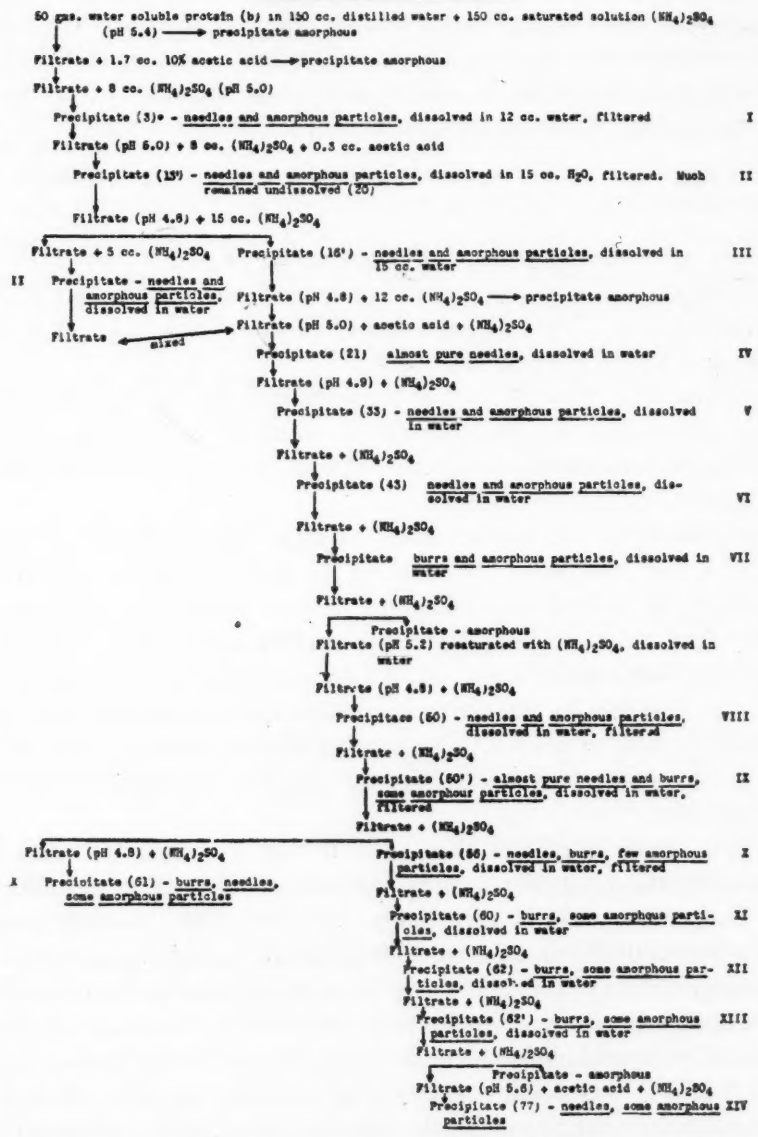
It was extremely hot weather when the experiment outlined in chart 4 was undertaken, and, as will be noted on the chart, half of the crystalline mass after the second crystallization became completely insoluble in water. This insoluble precipitate was washed with water and dried *in vacuo* at room temperature. A one per cent solution was then made of the dried protein by dissolving in dilute alkali and neutralizing with hydrochloric acid to pH 7.0. One-tenth milligram gave 5+ skin reactions in two tuberculous guinea pigs and negative reactions in two normal animals.

Ice-box temperature was then used during a subsequent trial for crystals, but the results, if anything, were less gratifying than at ordinary room temperature. It is very likely, however, that the spontaneous denaturization of the protein would be hastened by high temperature.

The importance of maintaining the proper hydrogen-ion concentration can be readily appreciated from a study of chart 4. Since the optimum condition for crystallization seemed to be a point or a very narrow range (pH 4.8–5.0) it was possible that the colorimetric method, which had been used, might not be sufficiently delicate and accurate. Through the courtesy of Dr. A. B. Hasting, the pH of the solution filtered from the crystals at the fifth crystallization was determined potentiometrically and was found to be (4.94, 4.89) average, 4.91. This checked very well with the colorimetric reading of 4.8 to 5.0 which had been determined as

Chart 4

Crystallization of Tuberculin Protein


50 gms. water soluble protein (b) in 150 cc. distilled water + 150 cc. saturated solution $(NH_4)_2SO_4$
(pH 5.4) → precipitate amorphous
Filtrate + 1.7 cc. 10% acetic acid → precipitate amorphous
Filtrate + 8 cc. $(NH_4)_2SO_4$ (pH 5.0)
Precipitate (3)* - needles and amorphous particles, dissolved in 12 cc. water, filtered I
Filtrate (pH 5.0) + 8 cc. $(NH_4)_2SO_4$ + 0.3 cc. acetic acid
Precipitate (13') - needles and amorphous particles, dissolved in 15 cc. H_2O, filtered. Much remained undissolved (20) II
Filtrate (pH 4.8) + 15 cc. $(NH_4)_2SO_4$
Filtrate + 5 cc. $(NH_4)_2SO_4$
Precipitate (16') - needles and amorphous particles, dissolved in 15 cc. water III
II Precipitate - needles and amorphous particles, dissolved in water
Filtrate (pH 4.8) + 12 cc. $(NH_4)_2SO_4$ → precipitate amorphous
Filtrate
mixed
Filtrate (pH 5.0) + acetic acid + $(NH_4)_2SO_4$
Precipitate (21) almost pure needles, dissolved in water IV
Filtrate (pH 4.9) + $(NH_4)_2SO_4$
Precipitate (33) - needles and amorphous particles, dissolved in water V
Filtrate + $(NH_4)_2SO_4$
Precipitate (43) needles and amorphous particles, dissolved in water VI
Filtrate + $(NH_4)_2SO_4$
Precipitate burrs and amorphous particles, dissolved in water VII
Filtrate + $(NH_4)_2SO_4$
Precipitate - amorphous
Filtrate (pH 5.2) resaturated with $(NH_4)_2SO_4$, dissolved in water
Filtrate (pH 4.8) + $(NH_4)_2SO_4$
Precipitate (50) - needles and amorphous particles, dissolved in water, filtered VIII
Filtrate + $(NH_4)_2SO_4$
Precipitate (50') - almost pure needles and burrs, some amorphous particles, dissolved in water, filtered IX
Filtrate + $(NH_4)_2SO_4$
Filtrate (pH 4.8) + $(NH_4)_2SO_4$
Precipitate (56) - needles, burrs, few amorphous particles, dissolved in water, filtered X
A Precipitate (61) - burrs, needles, some amorphous particles
Filtrate + $(NH_4)_2SO_4$
Precipitate (60) - burrs, some amorphous particles, dissolved in water XI
Filtrate + $(NH_4)_2SO_4$
Precipitate (62) - burrs, some amorphous particles, dissolved in water XII
Filtrate + $(NH_4)_2SO_4$
Precipitate (62') - burrs, some amorphous particles, dissolved in water XIII
Filtrate + $(NH_4)_2SO_4$
Precipitate - amorphous
Filtrate (pH 5.6) + acetic acid + $(NH_4)_2SO_4$
Precipitate (77) - needles, some amorphous particles XIV

* These numbers refer to the steps in the purification of the protein, and out of 90 of such stages only those are listed which led directly to the final crystalline product.

optimum. It may be that a most rigid adherence to the exact optimum pH, as can be determined only potentiometrically, may assist in increasing the yield of crystals.

After the tenth crystallization 0.1 cc. of fraction (56), containing, as shown later, 0.044 mgm. of coagulable protein (chart 4) was injected intracutaneously into guinea pigs with the following results:

Tuberculous	5+	Normal	negative
Tuberculous	5+		

The reactions in the tuberculous guinea pigs were readily recognized as tremendous tuberculin reactions, with extensive induration and necrosis in addition to the superficial scab which was found in the normal guinea pig, and was due only to the ammonium sulphate. The same suspension, tested after standing in the ice-box for two months, still gave maximum reactions.

One-tenth cubic centimetre amounts were also injected into the testicles of a tuberculous and a normal guinea pig. After six weeks these guinea pigs were killed and a true tuberculin reaction (12), with profound atrophy, was found in the injected testicle of the tuberculous guinea pig (figure 4), whereas the spermatogenesis was normal in the uninjected testicle of this animal (figure 5) and practically so in both injected and noninjected testicles of the normal guinea pig (figure 6). In this test, therefore, the immediate nonspecific reaction, due to the ammonium sulphate, is almost eliminated as a complicating factor.

As seen in chart 4, more needles were obtained from the filtrate from fraction (56), and although this suspension (61) was more sparse in needles it was also tested in guinea pigs (0.1 cc. doses).

Tuberculous	4–5+	Normal	negative
Tuberculous	died in tuberculin shock	Normal	negative

The reactions were similar to those described previously.

It had never been possible to determine or even estimate how much protein was present in the doses of the crystalline suspensions used, on account of denaturization during dialysis. The following attempt, therefore, was made, with this purpose in mind:

Two 5-cc. samples of the crystalline suspension (*56*) were boiled in order to coagulate the protein. The coagula were then filtered off on weighed, hardened filter papers, washed thoroughly with water, dried *in vacuo*, and weighed. Allowing for the gain due to hydration of the cellulose, the following weights,

FIG. 4

FIG. 5

FIG. 6

FIG. 4. SPECIFIC TUBERCULIN REACTION AFTER INJECTION OF 0.1 CC. OF CRYSTALLINE SUBSTANCE INTO TESTICLE OF A TUBERCULOUS GUINEA PIG

FIG. 5. NORMAL SPERMATOGENESIS IN THE UNINJECTED TESTICLE OF SAME TUBERCULOUS GUINEA PIG WHOSE INJECTED TESTICLE IS SHOWN IN FIG. 4

FIG. 6. NORMAL SPERMATOGENESIS IN TESTICLE OF NONTUBERCULOUS NORMAL GUINEA PIG INJECTED WITH 0.1 CC. OF CRYSTALLINE SUBSTANCE

due to the protein in 5 cc., were: (1) 0.00245 gm., (2) 0.0020 gm.; average, 0.0022 gm.

Therefore, in 0.1 cc. of suspension used for injection there was only 0.044 mgm. coagulable protein.

This was then compared with the amount of coagulable protein in 0.1 mgm. of the original water-soluble protein, which is the minimum amount needed to produce a maximum tuberculin skin reaction. Five cubic centimetres of a 1 per cent suspension was half saturated with ammonium sulphate and treated exactly as described above. The amount of coagulable protein was 0.00486 gm., which is therefore 2.2 times as much coagulable protein as found in a dose of equal potency of the crystalline fraction. The method of recrystallization has, therefore, succeeded in concentrating the active principle of the tuberculin.

A few drops of the crystalline suspension (56) were used for each of the following protein tests, with the results indicated:

Biuret	+	Ninhydrin	+	Molisch	negative
Millon's	+	Glyoxylic	+ (faint)	Vanillin	+

The purity of this protein fraction can be judged by the fact that the Molisch reaction is negative. The carbohydrate, which is found so consistently in the original water-soluble fraction, and which reduces Fehling's solution only after it is hydrolyzed with acid, has therefore nothing to do with the specific tuberculin activity.

Fraction (*56*) was recrystallized four more times, making a total of 14 crystallizations, when similar attempts were discontinued because of the increasing difficulty in crystallization and the almost complete invisibility of the crystals. This crystalline suspension was allowed to stand in the ice-box for six weeks and then tested on tuberculous guinea pigs. One-tenth cubic centimetre of the suspension was injected intracutaneously with the following results:

Tuberculous	5+	Normal	trace
Tuberculous	5+		

The reactions were so marked that there was no difficulty in classifying them as true tuberculin reactions even though superficial scabs were caused nonspecifically by the ammonium sulphate.

After a protein has gone through fourteen crystallizations, with a separation from the mother liquor each time, and when it shows an increased specific potency, as above illustrated, the statement appears

justified that the specific activity is due to the protein itself rather than to any hypothetical adsorbed impurity.

The specific rotation of the original water-soluble solution (*lot b*) (a 10 per cent solution) was −6.27°. When the reaction of the solution was at a pH of 7.0, even though the solution looked clear, the field was too dark to be read, and therefore some sodium hydroxide was added. On the addition of still more alkali the rotation changed to −5.88°. An attempt was made to ascertain the quantity of protein in the final crystallized fraction by determining its specific rotation, but this was found to be impossible, because the crystalline protein had become insoluble in water on standing. Much of this denatured protein was insoluble even in alkali, and when it was filtered off and dried on the filter paper a pink biuret reaction was produced on the paper.

Throughout this work it was noted that there was a shift in the solubility of the protein during manipulation. For example, originally the 126 gm. of protein had been soluble in distilled water, but after being taken down to dryness *in vacuo* at 40–45°C., the whole powder was no longer completely water-soluble. In working with the 50 gm. it was found that only a certain portion was soluble in distilled water at pH 5.4. Most of the residue, insoluble at this pH, was, however, soluble in distilled water at pH 7.0. The final residue, completely insoluble even at pH 7.0, was thoroughly washed and taken to dryness *in vacuo* at room temperature.

A 1 per cent solution of this residue was then made by dissolving in very weak alkali and neutralizing. One cubic centimetre of this, injected into guinea pigs, gave the following reactions:

Tuberculous	2+	Normal	negative
Tuberculous	1+		

This fraction, corresponding to the water-insoluble fractions reported in previous papers, is therefore practically inactive biologically, as were most of them.

DISCUSSION

Masses of evidence presented by many investigators, beginning with Koch himself, as well as all of the evidence from our laboratory, based upon chemical analyses, dialysis, precipitation and hydrolysis, and especially upon digestion by proteolytic enzymes, indicate very strongly that the active principle of tuberculin, which is responsible for the skin reaction in tuberculous subjects, is of protein nature.

In the case of tuberculin, as with other biologically active principles, toxins, etc., there has always been the question as to whether the specifically active substance is protein or merely an infinitesimal amount of some very highly potent factor attached to the protein. The difficulty in solving these problems has always been due to the fact that the purification of proteins is one of the most difficult chemical tasks there is. Only about a dozen proteins have so far been crystallized and none of these is from a bacterial source. A criterion of chemical purity of proteins is, therefore, very hard to establish, since crystallization and melting-point determinations are usually out of the question. Nitrogen analyses alone are not satisfactory, since the protein-decomposition products also contain nitrogen.

The evidence, however, presented in this paper, namely, that a water-soluble protein of the nature of an albumin, has been obtained from tuberculin in crystalline form and that this crystalline protein has undergone five, ten and even fourteen recrystallizations, without loss in its specific biological activity, leaves very little further doubt that the active principle in this case is protein. The protein is a product formed directly by the tubercle bacillus, since all of the tuberculin used was made in a nonprotein medium.

The high degree of purity of the protein after fourteen crystallizations may be judged by the great transparency of the crystalline mass, which appears as partially solidifying gelatine, and by the fact that the Molisch test for carbohydrate is negative, while the protein tests, such as the biuret, Millon's, vanillin, glyoxylic, ninhydrin and heat coagulation, are all positive.

The specific potency of the protein is furthermore increased by the purification process, since 2.2 times as much of the original water-soluble protein, calculated as coagulable protein, was required to give a maximum skin reaction, as of the protein recrystallized ten times.

The optimum crystallization point is pH 4.9, and the possible range of pH is extremely narrow. This detail in preparation is very important, but no more so than the fact that success in crystallization depends as much upon the art of manipulation as upon the addition of logical amounts of various reagents. The crystallization of ovalbumin demands some care and practice, but it is very much less difficult than the crystallization of tuberculin protein.

The extremely small yield of crystals and the great losses in activity occurring during isolation of the protein can be explained by the fact,

which has unfolded itself during these many experiments, that the protein is an extremely labile molecule, being readily denatured and undergoing chemical change accompanied by a decreased biological activity under the influence of certain common factors, which demand further study and exposure. In its most natural and unchanged form, it is crystallizable into needles and burrs, but with slight manipulation there is a small shift in the solubility of the protein or in its isoelectric point, so that while it was originally soluble in distilled water at pH 5.4, it becomes soluble only at a pH of 7.0. At this point the protein will not crystallize, but it will still give a maximum skin reaction. Soon the protein becomes completely insoluble in water, and requires a definite alkaline reaction to effect solution. This molecule has now lost also its biological activity; that is, it no longer gives the tuberculin skin reaction or kills tuberculous guinea pigs upon intraperitoneal injections of proportionate doses.

Along with the change in solubility and gradual biological denaturization there was observed another evidence of chemical change. The crystallized protein takes a purplish-blue stain with methylene-blue, and this is true whether the protein is in the form of crystals or small amorphous masses. As the protein becomes less soluble in water, it takes a deeper blue stain. Whether this observation will throw any light upon the difference in structure of the protein, accompanying a change in biological activity, awaits further study.

An appreciation of the instability of the specific protein explains why it is practically impossible to obtain pure crystals, free from amorphous particles by present methods. Moreover, it emphasizes the importance of using the least drastic methods possible when the highest yields of most potent material are desired, and explains why the protein, when isolated by means of ammonium sulphate, is far more potent than a protein denatured during precipitation with acetic acid or other acids.

Since, therefore, the specifically toxic factor in tuberculin is a protein, we are justified in interpreting the tuberculin reaction as an allergic protein reaction, and warranted in hoping for prophylactic and remedial results by truly immunological methods. The purity and chemical integrity of the protein may be very important factors in such experiments. The isolation from tuberculin of a specifically active protein in a state of chemical purity encourages similarly directed effort in the case of other bacteria.

SUMMARY

1. The specifically active substance in tuberculin, responsible for the production of the tuberculin skin reaction, is a water-soluble coagulable protein of the nature of an albumin, staining blue with methylene-blue, and containing the ordinary amino groups, but no carbohydrate, and crystallizable by Hopkins's method at an optimum pH of 4.9. Even after fourteen crystallizations the protein gave maximum tuberculin skin reactions and caused a typical tuberculin atrophy in the testicle of a tuberculous guinea pig. A test made after ten crystallizations showed that less than half as much of the purified protein was required to produce an equally strong reaction as of the original fraction.

2. The unit molecule of this crystallizable protein is, however, very unstable and easily becomes denatured. Such denaturization is recognized, first, by the facts that the protein will no longer crystallize and that its solubility is changed, and, second, by a loss in biological activity. This instability explains the small yield of crystals obtained and also the great losses in activity during the isolation of the protein.

I wish to express my gratitude to Dr. E. R. Long, through whom this work has been made possible.

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THE CULTIVATION OF TUBERCLE BACILLI WITHIN DIFFUSION MEMBRANES IN VITRO AND IN VIVO[1,2]

A Preliminary Report

P. C. HOU

One of the chief aims of this work was to cultivate tubercle bacilli in the animal body free from contact with tissue but living on the tissue fluid. It was also hoped that a large enough amount of bacilli could be collected in this manner for chemical analysis, to determine possible differences between bacilli grown in the body by this method and those grown on artificial media. All the available chemical analyses on tubercle bacilli are, of necessity, of bacilli grown on artificial media, since those growing in and responsible for the tubercle are too intimately mingled with tissue to be separated. Work has been done by Trudeau (1), Moussu (2), and others in the effort to grow tubercle bacilli in the animal body within diffusion sacs or filters, but all these workers used artificial media in their sacs before they embedded them in the animal body. I have tried to cultivate tubercle bacilli in semipermeable sacs without artificial media.

Before the actual work on animals was done, attempts were made to see whether tubercle bacilli will grow in empty sacs surrounded by an artificial medium. Freda Wilson (3) has shown that staphylococci may be grown readily in *Cellophane* sacs resting on artificial culture media without their passing through the sac-wall, while motile bacteria pass through. Three methods were used for this purpose in my experiments: (1) commercial semipermeable membrane (cellulose casing, an alkali-cellulose product used commercially as sausage casing [3]); (2) small glass tubes with a celloidin-covered window on one side, as suggested by R. H. Malone (4); and (3) parchment. The different methods and their technique follow.

[1] From the Department of Pathology of the University of Chicago.

[2] Aided by a grant to Dr. E. R. Long from the National Tuberculosis Association.

[3] Supplied by the Visking Corporation, through the courtesy of Dr. W. F. Henderson.

1: THE DIFFUSION-MEMBRANE METHOD

300-cc. flasks were filled with about 100 cc. of synthetic medium. Pieces of cellulose-casing tubing, about 15 cm. long and 1.5 cm. in diameter, were tied with strong thread at one end, and attached to glass tubing of 8 mm. diameter at the other. Leakage was tested by immersing the sacs under water and blowing gently into the sac through the glass tube. Air bubbles will come to the surface of the water if there is any leakage of the sac. The sacs were then put into the flasks with the blind end almost reaching the bottom of the flask. Cotton was plugged between the neck of the flask and the glass tube, in order to make the latter stable, and the mouth of the glass tube also was plugged with cotton. The flask and its contents were sterilized at 15 lbs. for 30 minutes. The flasks were kept slanted after cooling. This was easily arranged by cutting a card-board box at one side for the neck of the flask and keeping them in the box. The sacs floated on the surface of the fluid. Tubercle bacilli were then carefully introduced. Sacs containing fluid after the sterilization were discarded as leaky. Only those quite empty were used. The lump of bacteria introduced was laid on the inner surface of a part of the sac in contact with the fluid. The plug of the tube was not sealed with paraffin; so an abundance of fresh air entered the sac. The flasks were kept at 37.5°C.

Results

During the first week of cultivation no sign of growth appeared. After two weeks the growth became abundant and continued through the fifth week. At the sixth week the sacs were almost filled with dry tubercle bacilli. The inside of the sac still remained free from fluid. Outside of the tube the fluid was a little brownish, and had the peculiar smell of tubercle bacilli. Stained preparations from the growth in the sacs showed a pure culture of tubercle bacilli. After removal of the sac skin tests were performed on tuberculous guinea pigs. They all showed positive reactions, even on diluting the fluid with normal saline solution one hundred times. In some sacs slight growth continued up to ten weeks. When the fluid around them was centrifugated at high speed for 40 minutes, no tubercle bacilli were found in the sediment stained by the Ziehl-Neelsen method. The sediment was also injected subcutaneously into two guinea pigs, and the animals did not show any sign of tuberculosis six weeks after injection. Different protein tests tried on

this fluid, including the trichloroacetic acid, Millon's, the biuret, boiling, Spiegler's, the glyoxylic acid, and the Molish tests, all showed positive reactions. All the tests were controlled with pure synthetic medium and tuberculin prepared by the growth of tubercle bacilli on this medium. The reactions from the fluid from this experiment and from the standard tuberculin were always positive, while the pure synthetic medium reacted negatively. Obviously protein produced by the tubercle bacilli had passed through the sac in the ten weeks' cultivation, presumably the protein found by Long and Seibert (5) to be active in tuberculin.

The Method Applied in the Animal Body

Before this work was done Dr. E. R. Long embedded a cellulose-casing sac a foot long, containing tubercle bacilli, in the abdominal cavity of a hog. It was kept there for six months. Normally-staining bacilli were found in the sac after removal, but with slight if any evidence of growth. A large celloidin sac, embedded in the peritoneal cavity of another hog, sloughed out and was lost.

Technique: One end of a cellulose-casing sac was tied with thread, and the other end attached by thread to a glass tube of 5-mm. diameter slightly drawn out in the flame so as to permit secure tying, and the tubes were plugged with cotton. Each tube so made was put into a 12-mm. diameter test-tube, and cotton was plugged around its mouth, which extended into the open air. The entire apparatus was then sterilized at 15 lb. for 40 minutes. After it was cool tubercle bacilli were carefully introduced into each sac through the tube. As soon as this was done, the tubes were removed from their test-tube protection, and embedded under the skin, or in the abdominal cavity of guinea pigs, previously shaved and swabbed with tincture of iodine at the site of operation. Incision was made parallel with the spine, 2 cm. lateral to it, posterior to the last rib. The subcutaneous tissue was separated with a haemostat, which was pushed downward and backward, before embedding the tube. When the neck of the tube reached the line of incision, sutures were made around it, so that the cotton-stoppered end of the tube protruded from the skin. The site of incision was covered with 10 per cent celloidin, to hold the cut skin together. The cotton, which plugged the tube, was sealed with a small amount of paraffin to prevent evaporation. The intraperitoneal embedding was carried out in the same manner, except that the incisions were continued into the abdominal cavity, and

the tube was introduced into the peritoneal space. The peritoneum and the muscle were sewed up with catgut.

Results

The tubes, embedded subcutaneously, remained four to five weeks without causing necrosis of the skin, which at the site of operation appeared clean and dry. But a grayish-white caseous material accumulated in the neighborhood of most of the sacs deep under the skin, around the end of the sac as a rule. It did not appear to be the result of pyogenic infection. Smears prepared from it showed very few cellular elements. Many of the sacs were found broken. Three series of experiments were carried out, from 6 to 8 guinea pigs being used for each series. Eight embeddings were abdominal, and the rest subcutaneous. Three of the abdominal embeddings and two of the skin ones showed infection. Two of the subcutaneous embeddings showed distinct growth, but it was too small in amount for chemical analysis. The rest either failed, through perforation of the sac, or the lump of tubercle bacilli dried on the wall of the sac in a fold where no nutrition could be obtained. Some of the lumps were found even high up in the neck of the tube. This was probably due to the violent movement of the animals. A number of the tubes were sloughed out from the incision after three to five weeks. The intraperitoneal embeddings fared worse than the subcutaneous embeddings, the tubes being cast off even within a few days. The longest one we have kept in the abdominal cavity remained three weeks. But there was no sign of growth of tubercle bacilli. The tubes were soon surrounded by the omentum and were not perforated. The intraperitoneal pressure seems to be too high to keep them in the cavity.

2: THE METHOD OF A TUBE WITH A CELLOIDIN-COVERED WINDOW

This method has been described by Malone (4). Beautiful growth occurred outside of the body, when the tubes were immersed in a test-tube containing synthetic medium and the inside of the tubes was free from fluid. The method differed from that of Malone in that, after testing the leakage and permeability, I washed the tube with distilled water and sterilized it again in a test-tube which contained a few drops of water in order to keep the air inside moist. I did this in order to keep the inside of the small tubes free from any extraneous matter. Peptone solution, used by Malone to test the permeability, might also serve as a

medium for the growth of tubercle bacilli. Growth was abundant in six weeks. The fluid outside of the tubes remained clear, and contained no tubercle bacilli on examination after high-speed centrifugation.

This Method Applied in the Animal Body

Tubes containing nothing but small masses of tubercle bacilli were embedded in the animals in two different ways: (1) the tubes were completely sealed at the neck by a flame, and embedded intraperitoneally in guinea pigs; and (2) the tubes were not sealed, but embedded subcutaneously as in the first method.

Results

Three of the completely sealed tubes were embedded intraperitoneally. One removed after five weeks showed a small but unquestionable growth of tubercle bacilli. The inside of the tube remained dry and a small whitish friable mass was found on the membrane of the tube. Staining showed a pure culture of tubercle bacilli, and subculture proved its viability. It was cultivated on synthetic medium with 2 per cent agar, and very good growth occurred in three weeks. The other two, removed after eight and ten weeks respectively, were found filled with fluid, without sign of growth. The peritoneum was in each case smooth and glistening, and normal except for slight adhesions around the tube. The tubes were all surrounded also by rolled omentum. In one of these the pointed, sealed end of the tube had almost punctured the wall of the abdomen. Of 6 subcutaneous embeddings only one showed growth, and that slight. The others either showed no growth and were surrounded by caseous material, or the membrane of the tubes was perforated, and, as before, some of the mass of bacilli was found high up, attached to the glass wall.

3: PARCHMENT METHODS

Sheets of parchment were made into trays or boats, about 5 cm. long, 3 cm. wide and 1 cm. deep, attached to frames of glass rods. One end of each frame was joined with a glass tube about 6 mm. in diameter, through which tubercle bacilli could be introduced into the tray. These trays were placed in large-mouthed bottles of 300 cc. capacity, containing about 80 cc. of synthetic medium, and the mouth of the bottles stoppered with a cork, with the tube for inoculation protruding through

a hole in the cork. The preparations were sterilized as usual at 15 lb. for 30 minutes. After cooling, the bottles were kept horizontal. Tubercle bacilli were introduced through the inoculation tube into the bottom of the tray. The inoculation tube was stoppered as usual with cotton, but not sealed with paraffin.

Results

Excellent growth occurred in six weeks. The inside of the tray remained free from fluid, while the outside fluid was clear, but became a little brownish as growth proceeded. The fluid gave strong tuberculin reactions on skin tests. It remained free from tubercle bacilli, no bacilli being sedimented by high speed centrifugation. Attempts to apply this method to animals were unsuccessful, as it seemed to be impossible to make a suitable, nonleaking tube or a bag.

With this success in growing tubercle bacilli within diffusion membranes in synthetic medium, I attempted to grow them on animal organs and serum through membranes.

I: Brain: A brain was removed from a patient who died from aneurysm of the aorta. Autopsy was performed three days after death, but the body had been kept in good condition. There were no gross lesions in the brain. Pieces of the organ were removed both from the gray and white matter after separation of the meninges. These were ground thoroughly in a mortar and made into a paste. This was introduced into cellulose-casing tubes with one end tied with thread. After two-thirds of the sac was filled, the other end was tied on a 5-mm.-diameter glass tube, and the opening plugged with cotton. The tubes were prepared in this way in order to prevent bursting during sterilization. The sacs were then put into 35-mm.-diameter test-tubes. Glass tubes, about 4 cm. long and 5 mm. in diameter, were wrapped in cotton and inserted into the test-tubes. The outside end of each small glass tube was also plugged with cotton. About 5 cc. of normal saline solution was put into each test-tube in order to prevent drying. Sterilization was carried out at 15 lbs. for 15 minutes. The cotton at the mouth of the test-tubes was then impregnated with paraffin. The test-tubes were kept in a slanting position, and tubercle bacilli were introduced through the 5-mm.-diameter tube which protruded from the test-tube, and laid on the surface of the sac which contained brain material. The preparations were then kept at 37.5°C. Good growth occurred in three weeks.

This was enhanced by mixing the brain tissue with 5 per cent glycerol. The colonies were grayish white and wrinkled on the surface.

II: Blood: Preparations were made as above, except that defibrinated blood was substituted for brain. To each 4 cc. of blood 2 cc. of sterile Ringer's solution and 1 cc. of sterile distilled water were added, to make it hypotonic. The preparations were not autoclaved, as the blood was taken aseptically. Tubercle bacilli, inoculated on the surface of the sac and kept at 37.5°C., failed to grow even when glycerol was added to the blood.

III: Serum and Plasma: Liquid human and sheep sera were also used. Ringer's solution and distilled water were added as before, to make them hypotonic. The procedures were just the same as above described. Sheep plasma was also tried. Heparin solution was used to prevent coagulation and the plasma obtained by centrifugation. Ringer's solution and distilled water were added again to make it hypotonic. No glycerol was added to any of them. Very slight growth occurred in each case after four weeks, but it was almost negligible compared with that on the sacs which contained emulsified brain material.

CONCLUSIONS

All elements necessary for the growth of tubercle bacilli pass readily through diffusion membranes, whether the nutritive source be artificial culture medium or emulsified animal organ. It therefore seems quite possible that bacilli might be grown within the animal body by this method. Results obtained from animal embedding have met some success, but an improvement in technique is necessary for growth inside the body on a scale permitting study of the bacilli obtained. Experiments directed toward this improvement are in progress.

SUMMARY

1. Excellent growth of tubercle bacilli takes place within diffusion membranes, including cellulose-casing (purified cellulose) celloidin and parchment, without the passage of bacteria into the surrounding medium.

2. In six weeks' time tuberculoprotein, as shown by biological and chemical tests, passes into the medium surrounding the membranes.

3. Good growth occurs on ground human tissue when diffusion membrane separates the tissue and the growing tubercle bacilli.

4. In a few instances the cultivation of tubercle bacilli has been

achieved on a small scale inside of diffusion membranes embedded subcutaneously and intraperitoneally in guinea pigs.

The writer is very much indebted to Dr. E. R. Long for his kind help and valuable suggestions.

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A NOTE ON THE CHOLESTEROL CONTENT OF SPUTUM[1]

RUBY GREEN KELLY AND MAX PINNER

That sputum may contain cholesterol has been known for a long time. Biermer (1) in 1859 reported a patient, with an empyema perforated into the bronchial tree, whose sanguinopurulent sputum contained an enormous number of cholesterol crystals. Although he found a few cholesterol crystals on rare occasions in the sputum of phthisics, he was inclined to believe that large amounts of cholesterol are characteristic of perforated empyema. The same author quoted the observation made by Black (2) in 1853 on the occurrence of cholesterol crystals in the sputum of a patient with "pulmonary cellulitis with jaundice." Bokay (cited by Wells, Long, DeWitt (3)) found traces of cholesterol in sputum from bronchitis and from 0.141 to 1.617 parts in a thousand parts of sputum in pulmonary tuberculosis. Thissen (cited by Hoesslin (4)) demonstrated its occurrence in bronchiectatic sputum. Jakobsohn (cited by Hoesslin) found it in the ether extract of two tuberculous sputa. Bück (5) determined the cholesterol in five sputa from pulmonary tuberculosis; the daily expectoration of cholesterol was around 10 to 13 mgm. This author quotes Petters as having isolated considerable amounts of cholesterol from "bronchoblenorrhoic" sputum. This review of the literature is likely to be incomplete, but there are apparently no serial examinations on a larger group of various patients on record. Since the cholesterol in the sputum is most likely derived from cells, probably augmented under certain pathological conditions, it was deemed worth while to determine whether the amount of cholesterol in the sputum could in any way be in correlation with the clinical course.

METHODS

Since the volume of sputum depends to a large extent on the amount of saliva, and since the latter contains only a very small amount of solids, it was believed that more pertinent figures might be obtained by

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

measuring the amount of sputum by its dry weight. In control tests it was determined that autoclaving the sputum at 15 lb. pressure for 15 minutes does not alter the results. The thin serous parts of the sputa contain considerable amounts of cholesterol, so that it is necessary always to use the whole specimen. The mode of procedure finally adopted, after a series of preliminary trials, was as follows: The sputa were collected as 24-hour specimens; in some cases two or three days' specimens were used on account of the scarcity of expectoration. Each specimen was well mixed by beating with a glass rod and then autoclaved. They were then transferred into petri dishes and kept in a sterilizer at 100° C. until completely dry. Drying, as a rule, was completed over night. The weight of the total dry material was determined. Extraction was done in a Soxhlet apparatus with water-free chloroform for two hours. The chloroform was then treated according to the method of Meyers and Wardell for the estimation of blood cholesterol. The values determined are expressed in mgm. per gm. of dried sputum. The ratio volume in cc. of sputum to dried weight (in gm.) varied from about 10 to nearly 100.

RESULTS

The sputa of 59 patients with active pulmonary tuberculosis and of 10 patients with nontuberculous pulmonary lesions were examined. In summarizing the results the tuberculous patients were grouped according to the extent, to the pathologico-anatomical character of their lesions and in regard to the presence and absence of cavities. Table 1 presents a brief compilation.

TABLE 1

Cholesterol content of sputum in pulmonary tuberculosis, in mgm. per 1 gm. of dried sputum

		MINIMAL AND MODERATELY ADVANCED	FAR ADVANCED	PREDOMINANTLY EXUDATIVE	PREDOMINANTLY PRODUCTIVE	MIXED	CAVITIES PRESENT	NO CAVITIES PRESENT
Number of patients		13	32	25	23	11	43	15
Cholesterol content	Average	6.30	8.92	9.68	5.95	6.95	8.75	4.71
	Maximum	13.0	16.40	16.40	12.80	11.60	16.40	8.40
	Minimum	0.41	1.78	4.72	0.41	2.61	1.78	0.41

The average values shown in table 1 indicate that, with increasing extent of the lesions and with advancing tissue destruction, the cholesterol content of the sputum increases. It would seem, too, that the expectoration from exudative processes has a tendency to contain more

cholesterol than that from productive lesions. The maximal and minimal values, however, show that there exists a considerable amount of overlapping between the various groups, so that cholesterol determinations are not likely to afford reliable information in regard to the type of lesions and, thereby, to prognostication. That the general tendencies, mentioned above, do exist in a measure, becomes clearer by comparing two groups of patients, those with productive processes without cavities, and those with exudative excavating lesions. The values for the respective groups are shown in table 2.

TABLE 2

Cholesterol content of sputum in mgm. per 1 gm. of dried weight

		PRODUCTIVE PROCESSES WITHOUT CAVITIES	EXUDATIVE PROCESSES WITH CAVITIES
Number of patients		11	22
Cholesterol content	Average	4.67	9.83
	Maximum	8.40	16.40
	Minimum	0.41	7.10

By the method of classification as in table 2 the amount of overlapping is greatly reduced, the maximal values for the first group remaining below the average for the second group, and only overlapping with the minimal values in the second group.

The cholesterol content of 9 bronchiectatic sputa was determined. The average amount was 7.32 mgm. per gm. of dried material, the maximal 12.20 mgm., the minimal 2.50 mgm. Here again a wide variation is found. One pneumonokoniosis sputum contained 8.27 mgm.

From a further analysis of the data it was found that no relation exists between the amount of tuberculous sputum and cholesterol content, nor between the bacillary content and the amount of cholesterol, nor between the ratio, amount of sputum: dried weight of sputum, and the cholesterol.

On 9 patients the determinations were repeated at an interval of several months. In 3 patients the variation was less than 10 per cent; in the rest of the patients the changes observed reached nearly 100 per cent.

CONCLUSION AND SUMMARY

From the data presented above it is evident that the amount of sputum cholesterol has a rather definite, though not constant, relation to the type of lesions. Extensiveness, acuteness and tissue destruction make

for larger amounts of cholesterol. If one takes into account the fact that a qualitative diagnosis of tuberculous pulmonary lesions is difficult and uncertain to a degree, and that it involves a considerable factor of subjective judgment, the parallelism referred to above must be considered as a fairly close one. It is probably of approximately the same order as that of the so called "activity tests" (sedimentation reaction, Darányi and Matéfy reactions, etc.), and of differential blood counts, for all of which rather exaggerated claims have been made. A critical application shows for all these procedures (including the determination of the sputum cholesterol) that, at the best, they can confirm a well-balanced clinical judgment, but that they are hardly ever likely to secure information beyond that gained by clinical observation, physical examinations, X-ray studies and bacteriological findings.

We wish to acknowledge our indebtedness to Dr. W. I. Werner for valuable assistance.

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SOME OBSERVATIONS ON THE DEVELOPMENT OF PULMONARY TUBERCULOSIS IN LOWER ANIMALS AS COMPARED AND CONTRASTED WITH SIMILAR LESIONS IN MAN[1]

HERBERT FOX[2]

The most conspicuous and important manifestation of infection with the tubercle bacillus is that which occurs in the lungs. For this reason it is natural that much study and experimentation should be directed to explain why this tissue is so receptive of the virus, how it becomes diseased, the route of infection, the anatomical and physiological response to the morbid agent, and the course of the changing processes. Closely related, and really an inseparable part of all of these, is the opposition offered by the body, known as disposition, predisposition, resistance and immunity. In the course of investigations, special attention has been directed toward discovering whether these features of what has been called receptivity vary at different times of life, with the result that early in the history of the disease it was apparent that the youthful animal has the greatest receptivity, and is seldom immune. Starting from this knowledge there have arisen several theories as to the date of origin of all pulmonary tuberculosis in man, but especially that form usually called pulmonary phthisis, so well known to occur in late adolescence and early maturity.

The studies that form the basis of this paper were undertaken to discover whether anything could be learned in this direction by careful analysis of tuberculosis in wild animals, especially those zoologically related to man. It is, however, desirable, before describing the material, method of study and the peculiarity of tuberculosis in different varieties, to discuss the creditable current theories as to the date of origin and the events that lead up to recovery or death from the disease.

At this place there may be mentioned briefly that the methods of

[1] An address before the United States Live Stock Sanitary Association, Chicago, Illinois, December 1, 1927.

[2] Professor of Comparative Pathology, University of Pennsylvania, and Pathologist to the Laboratory of Comparative Pathology, Zoological Society of Philadelphia.

introduction of the tubercle bacillus into the lower animal's body are identical with those believed operative for man. Without entering the discussion as to the relative importance of the respiratory versus the alimentary pathway of infection, it can be stated that there is ample evidence that both are followed in the lower mammal as in man; my own figures would make them about equal for wild animals.

It is impossible to lead up to the subject of the time of infection and the theories that would explain it, without stating in a few words how the infection gets to the lungs. Tuberculosis does not behave exactly as acute infections usually behave, and it is nearly always impossible to determine the time of exposure that results in successful implantation of the germ. The entrance of the bacilli with dust and atomized saliva and sputum seems not a difficult matter to accept, since the direct penetration of the bacilli to the lungs has been followed. (Beitzke, Lubarsch-Ostertag, *Ergebnisse, etc., 1910, no. 14.*) Anthracosis of the lung and its related lymphatic tissue must be explained in the same way. The often greater extent of tuberculous lesions in the lung has been taken to indicate the origin there, but it is quite possible that a massive lesion may exist at a secondary deposit and a trifling one at the immediate atrium. Nor does the almost invariable involvement of the lymph nodes about the bronchi and trachea help much, for this tissue is one for which the bacillus has an especial predilection, notably in youth, as it almost never escapes without morbid changes, no matter how the germs enter. The settling of tubercle bacilli on the mucosa of the bronchial wall may be followed by their penetration to the rich lymph-vessel plexuses that ramify through the lung and along which they may be carried by phagocytes or by the lymph-current. As we shall see, tuberculosis, of youth at least, is a disease of the pulmonary tissue, and of the lymph nodes; these foci may or may not be related in the matter of lymph drainage. It is possible that on some occasions bacilli penetrate *via* the lymphatics to the blood circulation and are redistributed to the lungs; but this cannot be the rule. There might be mentioned in this connection that experimental haematogenic infection results in tubercles at the edges of the lungs and beneath the pleura, the lymph nodes and middle pulmonary parenchyma often escaping.

The alimentary tract would seem very important as an atrium of infection, especially in the lower animals that lick objects, soiled by the discharges of other infected ones. Tubercle bacilli certainly can enter the intestinal wall and perhaps leave no trace at the point, but the

drainage line would contain evidences of their action. Von Behring's theory holds as a strong point this traceless entry, especially in infants when the mucosa is incompletely formed and very permeable. Once within the body the path followed would lead to the venous circulation rather than to the bronchial and tracheal lymph nodes and the pulmonary parenchyma.

With these brief statements of the two sides, let us pass for a space to the question of how receptivity influences the events that follow invasion. It has always been accepted that if an affected animal be very susceptible, progressive degenerative and caseating lesions arise. On the other hand resistance is expressed by fibrosis and calcification. It is acceptable that tuberculosis in human youth, in very susceptible adults and in certain sensitive lower animal varieties proceeds rapidly to the formation of degenerative inflammations or large caseous masses. So definite a picture does this present in young children and so much does it resemble the disease in monkeys that the pathological complex has been called "monkey tuberculosis." So, too, one finds repeatedly quoted in literature the susceptibility of aboriginees (Indians, Esquimaux) to the tubercle bacillus, the morbid lesions in them resembling the just-mentioned groups. So definite is this idea that when the lesions do not progress thus, resistance or immunity is predicated. Is such lack of response to the tubercle bacillus a natural one, or one due to previous infection and the development of a certain grade of immunity? Many sides of this part of the subject are open for thought.

The natural response is based on what is termed disposition, and differs in different animal orders and even in different members of closely related species. This applies not only to actual incidence of disease but to the form in which it develops. Thus, for example, certain breeds of cattle are less susceptible than others. South American monkeys are definitely less susceptible than are African varieties, although more often used as household pets. The American opossum, an occasional pet, is resistant to tuberculosis, while the disease has, to my knowledge, not been seen in its ordinate relative, the kangaroo. Many other examples might be given. The type of disease may be peculiar in other orders than *Primates*. Thus, for example, the nodular caseous or fibrocalcareo-caseous masses of the *Ungulata* are well known, the domestic cow offering a good example. Chronic ulcerative lesions are characteristically found in the order *Carnivora* and in the *Equidae*.

If now one would study the tissue reactions of these orders and groups somewhat more intimately, the use of the classification of tissue resistance by Theobald Smith (*Jour. Am. Med. Assoc., 1917, lxviii, 764*) may be of value. He states that the best evidence of tissue resistance is the giant cell; then in order he puts the following: (2) giant cell with an epithelioid mantle remaining pervious without necrosis and tending to sclerosis; (3) a larger similar process with caseation and calcification; (4) a group of tubercles due to unhindered bacillary growth forming a relatively large focus with the usual retrogressive (degenerative?) changes; (5) rapid and copious multiplication of bacilli within a focus with necrosis and multiplication. Opie (*Amer. Rev. Tuberc., 1922, vi, 540*) suggests that cavitation may be an indication of resistance. Throughout all his work, to which extensive reference will be made shortly, Opie refers to fibrosis and calcification as resistance or immunity phenomena of individuals without making it peculiar to man.

Having recently reviewed many gross and microscopical preparations, having in mind the rules of Smith and of Opie, it appears that the order *Primates* below man exhibits certain very definite features that correspond to these observations. In the first place the bare giant cell is practically unseen in the monkey and ape. Caseation is common, while calcification is exceedingly rare. The chief anatomical lesion corresponds with Smith's fourth grouping,—unhindered bacillary growth, few giant cells and degeneration. The susceptibility of these animals is further shown by the infrequency of cavitation or of that fibrogranulation-tissue wall that makes a cavity possible.[3]

Still further analysis of the order *Primates* reveals that the families *Simiadae* and *Cercopithecidae* are most susceptible as to incidence and tissue reactions. The family *Cebidae* (South American monkeys) have inconspicuous yet well developed pulmonary lesions, but definite lymphatic disease. The incidence in this group is definitely lower than in the first two, but their lesions are firmly caseous. The lowest family of *Primates* (*Callitrichidae* or *Hapalidae*) have shown no tuberculosis in the 57 specimens at our disposal.

If now we pass to the *Carnivora* a very definite change of incidence and anatomy meets us. Tuberculosis occurs among the domestic carnivores

[3] The only actual fibrous-tissue formation known to the author occurred in a pair of monkeys that had received living tubercle bacilli as an immunizing measure by Dr. Gerald Webb; the fibrous reaction did not, however, greatly influence the outcome of the disease. There was no calcification.

with reasonable frequency (3–5 per cent among dogs, 0.5–2 per cent among cats, according to statistics). Among the wild carnivores it has been reported frequently throughout the world, and always with the same picture,—a chronic ulcerative process, which in the lungs characteristically forms large masses with fibrocaseation or with cavity, or with both. More closely studied, the tuberculous tissue is found to consist of epithelioid cells and small mononuclears with very few giant cells. The resistance of *Carnivora* to tuberculosis is surely not indicated by a large number of giant cells. Opinions differ as to their frequency. I have seen them several times. Douville states that they do not occur in canine tuberculosis. Calcification varies greatly; its presence may be sought in the pleural wall of dogs, but it has not been seen in our wild specimens. The carnivores, therefore, seem to lack two accepted evidences of resistance, namely, giant cells and calcification, although they do not have great susceptibility to the disease, as would be indicated by frequent occurrence or widespread degenerative lesions.

The order *Ungulata* presents very remarkable receptivity and resistance to tuberculosis. The domestic *Bovidae* show this, although they are too closely associated to domesticity for us to accept them as representing what may be true for wild ungulates. All varieties of this order receive the infection and their reaction is closely similar in all the families. Giant cells are numerous, fibrous tissue and caseation are almost invariable, calcification is the rule, and cavitation uncommon; this is a combination of characters that would indicate a marked resistance, and yet true healing or perfect limitation of lesions rarely, if ever, occurs.

The order *Marsupialia* is instructive for reasons already given and because we have observed two cases of the disease in the opossum, animals that had been presented from private sources and had lived in the company of human beings for several months. These animals showed abdominal lesions only, caseous degenerative foci made up of soft granulation-tissue with few giant cells. The lungs were not involved. Two cases are insufficient for general observations. It, however, seems noteworthy that among 325 autopsies upon marsupials only these two cases should have been found, and in animals exposed closely to man.

The remaining zoological orders among the *Mammalia* have supplied too few cases of tuberculosis to permit of inclusion in this study. The response of the human being, having been most studied in regard to age, will be discussed in connection with Opie's work, since the subject is put most concisely by this author.

It appears from the foregoing that the response of various animals is definitely peculiar to the groups. Certainly there is a difference in receptivity and in pathological prognosis between lower *Primates* and *Carnivora*, between *Ungulata* and *Marsupialia*. There is fair reason to assume that the lesions as they appear in a zoological collection are natural responses to first exposures, since there is no evidence that tuberculosis exists in the wild, and therefore one cannot argue that the form of receptivity is modified by previous exposure. It has been repeatedly stated that the usual form of tuberculosis in man is due to the long standing of the disease among man and a certain grade of hereditary resistance or a survival of the fittest. In domestic cattle it has been assumed that the resistant animals have been kept, the poor ones killed, and a more resistant animal breed developed. Is it not reasonable to view both man and bovines as having a specificity of response to infection? How will the theories as to the time of infection help us and how will wild-animal observations fit with those on man?

Tuberculous infection has been shown to exist in a very large percentage of individuals, Opie stating that 98 per cent of adults dying from diseases other than tuberculosis have healed or focal lesions somewhere in the lungs. The infection can be demonstrated by tuberculin tests and X-ray pictures of the chest in an increasing percentage as age advances. Infancy and youth are the age periods when the body is most receptive of the bacillus, as has been shown clinically and experimentally. The intestinal wall of the infant is easily permeable. Infection of human adults is apparently difficult, as indicated by the infrequency of marital transmission, and of evident contagion to the personnel of tuberculosis sanatoria. Inoculation of animals does not lead to a disease like human phthisis, which fact may be explained by the varying natural reaction of experimental animals. Small doses of attenuated bacilli given repeatedly to certain animals may result in a lesion suggestive of human consumption. Inoculation of bovines always results in a typical bovine tuberculosis. An animal once infected with tuberculosis, if inoculated again, will experience no increase of its original focus of disease and at the site of the second injection will show an inflamed area that soon heals.

Using these accepted data, von Behring (*Tuberculosis, 1907, vi, 423; Bekämpfung der Infektions-Krankheiten, 1912*), an ardent supporter of the theory that tuberculosis begins as an alimentary infection, devised the theory that all tuberculosis originates in infancy or childhood from contact with an infected person, or swallowing infected food. Infection

passes *via* the cervical and mediastinal lymph chain to the tracheobronchial lymph nodes, and thence along the intrapulmonary septal channels to the apex. Or it may ascend from abdominal lymph nodes to the mediastinum or even penetrate to the circulation, thus to be distributed and to find its most favored locus in the apex. Sometimes these foci heal; at other times they only remain latent. In later life under a variety of conditions, von Behring believes that these foci awaken to activity. It may be that the healing of the original foci is attended by an increased local and general resistance, but this is never complete enough and redevelopment may occur. At all events, an animal or man reinfected with tubercle bacilli, or experiencing an extension, has a different reaction than on the primary occasion, the most notable difference being that primary tuberculosis is chiefly a lymphatic response, secondary lesions being more in the parenchyma.

This question of the time of infection has been dealt with in a series of papers by Opie (*Jour. Exp. Med., 1917, xxv, 855; xxvi, 263; Amer. Rev. Tuberc., 1922, vi, 525; 1924, x, 249; Jour. Am. Med. Assoc., 1927, lxxxix, 1293; Arch. Path. & Lab. Med., 1927, iv, 1; Trans. Coll. Phys., Phila., 1927*). The course of this work and the concluding theory may be summarized as follows:

Tuberculosis of infancy and childhood is usually a disseminated process within the parenchyma of the lung. It is always associated with lesions in the tracheal or bronchial lymph nodes. When the process is active and progressive, it is usually unicentric. Very young children show much caseation while fibrosis appears in older children.

Adult tuberculosis is of two types. The first is a fibrocaseous ulcerative or perhaps calcifying process, usually at the apex and not associated with caseous lymph nodes. The second type is focal, with circumscribed or limited masses scattered variously in the body of the lung and associated, sometimes directly, with a caseous lymph node. They rarely exceed 1 cm. in size, and may be single or in a localized group. This form is probably the unresolved lesion of infancy and youth, and increases in incidence so that at 30 years 85 per cent of people have these foci. Focal lesions are not related to the chronic phthisical apical lesions, either anatomically or by lymph-drainage, for they may occur in opposite lungs. Focal lesions tend to heal; phthisical lesions do not. Opie suggests that the more evident the inactive focal lesions, the less active the apical phthisis. Focal lesions may occur at the apex, where they produce a scar or fibrocalcareous mass in the lung tissue; pleural involvement is not necessarily tuberculous, but should be examined carefully.

Childhood tuberculosis forms scattered lesions in no particular part of the lungs, but always involves the parenchyma and, to repeat, is always associated with lymph-node lesions. While no tendency to heal appears early, as the child grows older more and more calcific foci appear at places known to have been focal lesions. Between 50 and 70 years, over 90 per cent of all persons have calcified nodes in the lung proper. Intestinal tuberculosis usually leaves some trace in the abdominal lymph-drainage area, and where these are prominent few pulmonary foci are found.

Opie thinks that the evidence at hand is amply convincing to accept the origin of intrapulmonary lesions by inhalation of germs and that they are more extensive than those produced by feeding tubercle bacilli. However, he agrees with Calmette and with Smith that the lymph nodes may be attractive or nonresistant to tubercle bacilli which may set up a slowly progressive process that may later spread to the parenchyma of the lung. Slowly progressive lesions at any place may afford some resistance to secondary infection. "It is seldom if ever possible to demonstrate by anatomical examination, that apical tuberculosis of adults has spread from a focal lesion of childhood. . . . Focal lesions which become encapsulated and tend to heal are not associated with cavity formation and do not cause the dissemination of bacilli." Tuberculous lesions at the apex may go into a fibrous stage without cavity, and are found in 15 per cent of persons not dying from tuberculosis. A puckered scar *in the lung* and pleura may be found in 22 per cent of such people. *With all these apical lesions there are found numerous calcified foci scattered through lung and hilum lymph nodes, and the more numerous the scattered foci the less active is the apical process.* These calcific areas are more numerous in persons who have no active lesions, and who die from some other disease than when progressive tuberculosis coexists. As age advances calcific areas become more numerous. Fibrocaseous areas of focal type show more tubercle bacilli than do fibrous scars. Fibrous scars at the apex may not have the microanatomy of a tubercle. Calcific areas rarely contain tubercle bacilli, but if focal or apical lesions exist in the lung the bacilli are found in the lung tissue about the calcific areas.

As one examines bodies at all ages it seems certain that nearly every child has some tuberculous infection, that in adolescence focal lesions become increasingly more numerous, that apical lesions of a different sort unrelated anatomically also increase and that one can find every transition from healed to latent to fatal infection. Parenthetically I might interpose here that this is true in wild animals only in part and in one variety, the *Ungulata*, which have a very peculiar response to tuberculosis. Opie proceeds to state that experimental tuberculosis is similar to that in man only when the animal has been made somewhat resistant by preliminary infection, and the result then finds an analogue in adult apical human phthisis.

Opie has collected this formidable array of data by long study of extensive material, which he has supplemented by roentgen photography of lungs removed from the chest. By this means he has been able to discover the disseminated calcific foci in the parenchyma of over 90 per cent of persons not dying of tuberculosis. On the basis of his studies Opie has evolved the following theory of the origin of that form of tuberculosis known as adolescent and adult phthisis:

> Nearly every child is infected; many succumb; but, if they survive, there remain foci in the lung that become calcified and the bacilli die off in the course of years. Some foci do not perfectly heal, but remain as fibrocalcareocaseous or mortar-like masses, called latent focal lesions; these may later reawaken to activity. Adult apical phthisis is a secondary or superimposed infection, unlike juvenile tuberculosis, and is the result of the action of the tubercle bacillus in a person who has acquired resistance by recovering from infantile or childhood infection. When tuberculous infection occurs in an adult who has no evidence of having had juvenile lesions of a calcified or focal type, the resulting morbid anatomy resembles that seen in the disease of earliest life, and is quite rapid in its course. Opie, therefore, thinks the theory of von Behring to be disproved, that adult phthisis does not date from childhood, but develops in an individual prepared by recovery from infection in youth.

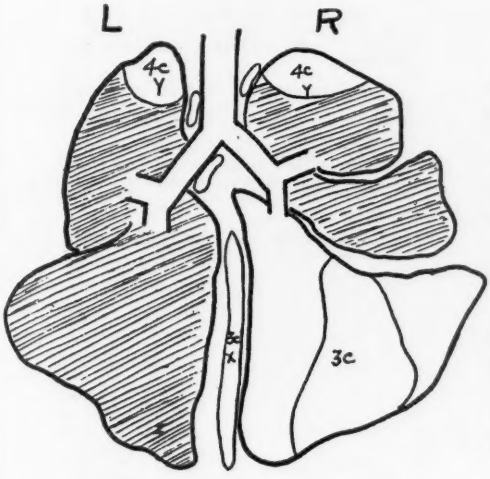
Studies of a similar kind have been made by H. H. Scott (*Proc. Royal Soc. Med., Sect. Comparative Medicine, 1927, xx, 2, 197; Annals Tropical Medicine & Parasit., 1921, xv, 213 & 381,* and personal communications). He made his observations on children of the Chinese who may be considered as presenting a very fertile soil for the bacilli. This observer emphasizes the wide distribution of juvenile foci. He shows further that juvenile foci are anatomically related to lymph-node lesions, but shows that this often implies a single or unicentric process. However, careful search will always reveal lymph-node lesions if intrapulmonary foci are found. This need not be true for adults. He concludes further that when the atrium of infection is not in the respiratory tract (in the intestinal area, for example) the pulmonary disease is insignificant or may not exist; whereas, when there is no other evident portal of entry than the lung, the lung shows the major lesions. Scott, in applying his knowledge to a study of wild animals, finds it difficult to decide upon the atrium of infection, because in most varieties of animals generalization occurs more rapidly than in man and the reaction or receptivity is quite variable. He states that since they are virgin soil, the progress is rapid, the course peculiar, and there is no evidence of healing. He has seen

calcification only in ungulates, never in monkeys, and he states in a letter that he has never seen what might be considered as evidence of healing in these latter animals. Carnivore tuberculosis, according to Scott, is parenchymatous and not lymphatic; this is also my experience. A revision of our carnivore tuberculosis reveals that only in the *Procyonidae* are the lymph nodes always involved to any extent. Among the eight cases in the *Ursidae*, *Felidae* and *Viverridae*, naked-eye lesions in lymphatic tissue are recorded only twice. In two animals, a jaguar and a bear, it is specifically stated that no lesions were found in the hilum lymph nodes in the presence of active bronchogenic nodular caseous tuberculosis.

The foregoing observations and theoretical considerations have been applied to a study of tuberculosis in the animals at the Philadelphia Zoological Garden, with the hope that comparative study might throw some light upon the subject. The principal features that have been investigated are the evidence of healing, the existence of calcific, focal and advancing lesions, the importance of calcification, the relation of lymph-node and parenchymal lesions, the position of retrogressive and active lesions, and the relative importance of alimentary-tract infection. This last has not been very satisfactory in result because of the reasons already credited to Scott. The manner of carrying out the investigation was modelled after that of Opie,—the X-ray photography of excised lungs. The results have not been very satisfactory, but some points have been learned. I wish to register here my thanks to Dr. H. K. Pancoast and his associate Mr. Jamison for their efforts to obtain successful pictures of these lungs. After removal from the body they were photographed as soon as convenient, being blown up by a bulb and catheter introduced into the trachea. The excised pulmonary tissue offers so little resistance to the X-ray that clearly reproducible pictures are not easy to obtain, but several excellent films have been available for study. This method being limited in usefulness and since every lung had to be carefully dissected, it was thought that very thorough slicing and palpation would reveal all the pathological changes in the lung, especially when supplemented by microscopic-section study; this technique Dr. Opie approved as satisfactory to demonstrate calcified, focal and progressive lesions, if done thoroughly. Since beginning the study, we have had available 10 *Primates*, 1 *Carnivora*, and 7 *Ungulata*. Besides these freshly dead animals there have been found in our jars 13 monkeys,

2 *Carnivora*, 2 *Ungulata* and 1 *Marsupialia*, all of which have been subjected to the same careful sectioning. A graphic lung chart has been made of every pair of lungs when usable lesions were found. In addition, records and data from our postmortem protocols have been used when necessary; the two sources are quoted independently since the method of study has necessarily been different.

1: Evidence of Resistance: The criteria of resistance that tends toward healing will be fibroid encapsulation, calcification, cavity-formation and



572 Rhesus Macaque ♀ (Macacus rhesus)

Gave positive reaction to tuberculin test and died two months after arrival. Pneumothorax from cavity. No retrogression of any part.

Left lung beset with single and small conglomerate tubercles and small areas of infiltrate. Some bronchiectasis. As one passes from apex to base, lesions become firmer, older, more circumscribed and seem shot-like to finger. No true fibrosis or calcification. Pleural thickening over lower lobe only.

Right upper lobes correspond with left lung. Lower lobe wide area of caseation, remainder of lung with a very few scattered precaseous nodules. General pleural thickening.

Description of Lung

x - Large caseous mass in middle mediastinum from lymph gland below left bronchus.

y - Acute ulcerative with cavity.

z - Hardest nodule, but not calcified.

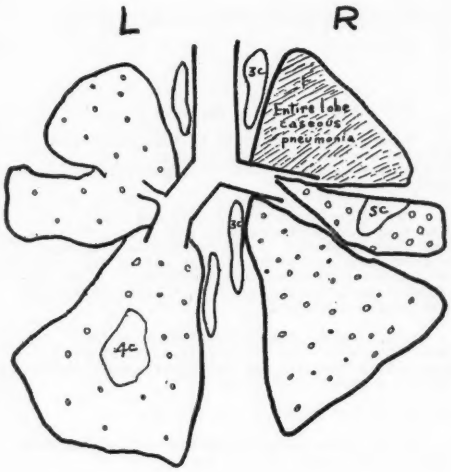
1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary

a. Small spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading

FIG. 1. CASE 1. TO ILLUSTRATE OLD FOCI, ONE IN LEFT LOWER LOBE AND ONE IN THE INFERIOR MEDIASTINAL GROUP

giant-cell formation. Fibroid encapsulation is found only in carnivores and ungulates. It is never complete and tubercle bacilli in goodly numbers may be found in such foci. A fibrosis in a capsular form is characteristic of all lesions in the ungulate, except the rapid caseous pneumonia. Calcification, although to be mentioned in this heading,

is appropriately discussed in full in the next two sections. Cavity-formation is found in the carnivore, ungulate, and, rarely, in the monkey. In the last-named animal, it should be emphasized, the cavitation is due to a removal of a large mass of recently produced necrosis and is not the result of slow ulceration and discharge, the space being surrounded by recent slough and not by granulation tissue with exposed blood-vessels, a picture well known in the carnivore and in man. Chronic cavitation is,



993 Green Monkey ♂ (Cercopithecus callitrichus)

This animal was tested four times from June 22, 1906 to January 14, 1907, but never passed. All viscera except intestines are involved.

Some tuberculous mediastinitis, perisplenitis - not in spleen. Miliary nodule in liver. None in mesenteric glands, or at coeliac axis.

Entire left lung beset with gelatinous and precaseous tubercles, pin point to 4 mm. No nodules other than drawn. No calcification or foci.

Except as marked, the right lung is beset with tubercles as on the left.

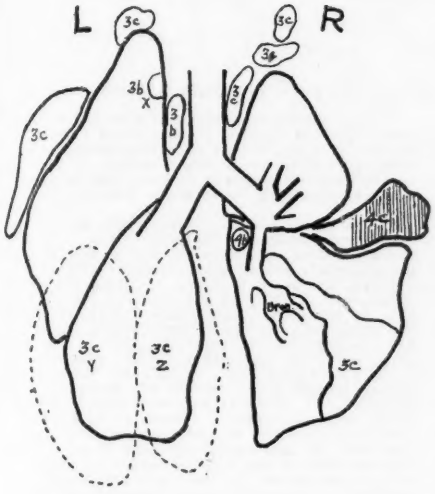
1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary

a. Small spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading

FIG. 2. CASE 2. TO ILLUSTRATE OLDER FOCI IN LEFT LOWER LOBE AND IN RIGHT BRONCHIAL LYMPH NODES ON THE SIDE WITH RECENT DEVELOPMENTS; AN INSTANCE OF AEROGENIC TUBERCULOSIS

therefore, an expression of tuberculosis in man, carnivore and ungulate. Giant-cell formation, aside from miliary tubercles, was carefully sought in these monkeys and one ungulate recently dead, and in older sections of 10 various members of all three groups discussed in this paragraph. No separate giant cells were found. More giant cells were found in the tuberculous tissue of ungulates and monkeys than in the tissues of carnivores.

2: The Existence of Calcified and Focal Lesions: As has been stated, calcification is characteristic only of the ungulates. Among the 38 well-studied lungs, it has occurred once, in a raccoon, in the form of disseminated foci as described by Opie. These nodules did not contain bacilli or histological tuberculosis, and, as the animal showed no evidence of tuberculosis and no instances of the disease have been encountered in raccoons, one must consider them either multiple parasitic remains



1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary

a. Small spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading

2737 Schmidt's Monkey ♂ (Cercopithecus schmidti)

This animal with its mate arrived at the Garden April 24, 1912. Both passed the tuberculin test, but the mate died July 8, 1012 with general tuberculosis. This test was a failure because we paid too little attention to delayed reactions.

This monkey was quarantined until September of the same year, retested and failed. It was killed Oct. 12, 1912. Lesions were not so old, or at least not so advanced as in the description of the mate, the organs of which were not saved. No calcification. Diffuse tuberculosis of spleen, tuberculous colitis and pericolitis tuberculous proctitis and periproctitis. All active, productive in type. No other tuberculosis than mentioned to be seen grossly.

All areas on right side are intrapulmonary.

Description of lung.

x - Intrapulmonary.

y - Partly extra-, partly intrapulmonary caseous mass that combines with-

z - A large exprapulmonary mass that originated in mediastinal lymph nodes. These are surrounded by dash lines.

x y - Only intrapulmonary tuberculosis on left side.

No scars.

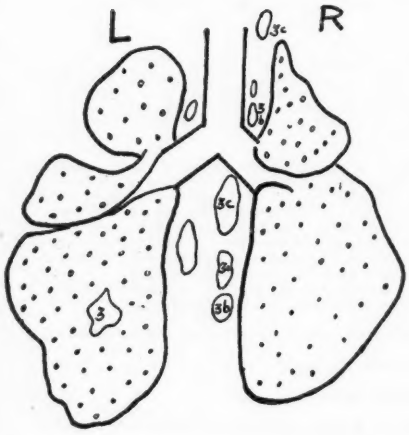
FIG. 3. CASE 3. CASE OF ABDOMINAL INFECTION WITH MEDIASTINAL AND PLEURAL TUBERCULOSIS AND RELATIVELY LITTLE PULMONARY INVOLVEMENT

(which sometimes occur in these animals), which is probably correct, or as healed tubercles. In none of the monkeys was there calcification within the lungs or lymph nodes.

Focal lesions were encountered only in monkeys and most definitely developed in the old-world varieties. The *Cebidae*, a family with low receptivity for tuberculosis, showed no calcification and no very clear

focal lesions. However, in one example (*Cebus apiculatus*, fig. 8) there are older, somewhat limited caseous areas in the left lower lobe and left tracheal lymph node that might have been foci whence spread occurred. Among the ten old-world monkeys, there were four examples (1, 2, 4 and 7) of well-defined focal lesions with firm caseation, apparently older than the remaining tuberculous lesions. (Fig. 7.)

3: Importance of Calcification: Judging by the data just presented and by a study of our general material, calcification *per se* does not appear



1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary
a. Small spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse, spreading

3863 ♀ Rhesus Macaque ♀ (Macacus rhesus)

This animal was presented July 10, 1911 from a private family. Her young lived 19 months, dying 4 days after the mother, and showing no evidence of tuberculosis. The organs were not minutely studied, but no gross lesions suggesting tuberculosis were found.

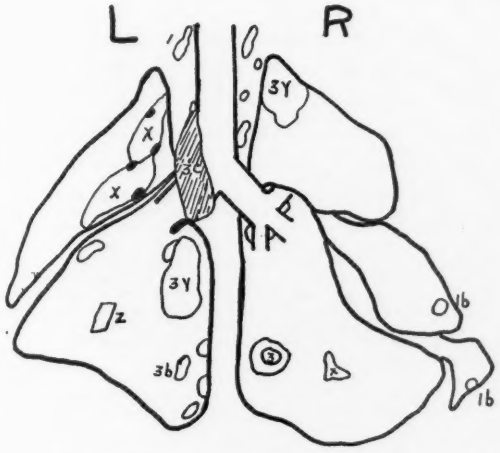
The costal pleura shows several several subpleural nodules of the pearl type. The lungs lie free and are studded with subpleural and internal, yellow-gray, sharply outlined nodules, pin point to 3 mm. There are no adhesions. Only at one place in the left lobe is there any conglomerate formation. The lymph nodes of the interpulmonary region are involved only on the right side. These lymph nodes are the only ones that show distinct soft caseation. All other tubercles and masses are firm, unsoftened, caseous material. There is no cavitation. There is no bronchiectasis. There is no perceptible calcification at any place. The original seat of tuberculosis appears to be a large caseous mass in the coeliac region. There are caseous masses in the liver and lesser omentum. Adhesive tuberculosis of diaphragm and liver. The splenic nodules seem to be all immediately subcapsular. This case appears to be a bovine infection of alimentary origin. Primary involvement of the abdominal lymph nodes, disseminated intrapulmonary tubercles.

Histological section shows the lung lesion to be the conglomerate, rapidly advancing tubercles with infiltration of the surrounding parts by large mononucleares. There is no sign of retrogression in any part of the section.

FIG. 4. CASE 4. OLDER FOCI IN LEFT LOWER LOBE AND IN RIGHT LYMPHATIC NODES FOLLOWED BY MILIARY TUBERCULOSIS

to be a very valid criterion of resistance to tuberculosis. Examination of the records of kangaroos and rodents failed to reveal its presence in healed foci, and these animals have been in the collection in sufficient number and have been as much exposed to infection as ungulates or carnivores. The calcium metabolism of animals in a menagerie is often in a state of imbalance, and metastatic calcification to the lungs might be expected. There are copious examples of bone dystrophy among our

specimens, but calcium deposited in the lungs is not a prominent feature. However, in youthful animals, especially when infested with parasites or suffering from nonspecific respiratory infection, it is highly probable that calcium would be deposited at foci of irritation without implying that tubercle bacilli had started the nidus. This may be true for the human being in youth, when the calcium of the food is very rapidly



1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary

a. Small spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading

8228 Mandrill Baboon ♀ (Papio maimon)

In the Garden five years, isolated because of poor condition for one year. Passed the tuberculin test in 1921 and again in 1923. In good condition at that time.

This tuberculosis suggests bovine type especially because of pleural and peritoneal masses. Practically all viscera were affected. There are no calcific nodules. The most progressive area is in the left bronchial gland.

Description of Lung

x - Pleural thickening with fibrous nodules.
3 - Surrounded by pleural thickening
3y - Entirely pleural
z - Thickened small bronchus

Bronchi filled with coagulum.
Irregular fibrosis of lateral lymph node between esophagus and trachea.
The areas 1-b are the only ones within pulmonary tissue - others all pleural and separable.
In left lung only lesions in pulmonary tissue are 3-b near the tip of the lower lobe. Other foci all in pleura and separable.
Lesions suggest bovine type. The disease is lymphatic - only six lung scars and fibrocaseous nodules in pulmonary tissue.

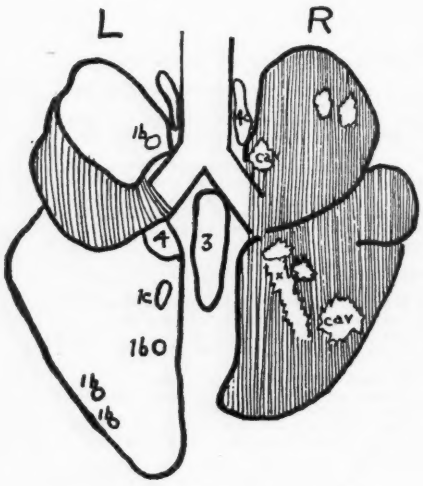
The pleural and subpleural foci are chronic fibrous thickenings of a loose nature, but without tubercles. Within the lung proper there are no old areas, but there are two spots of obliterated endarteritis. There is marked anthracosis with fibrosis, and there is distinct chronic bronchitis.

FIG. 5. CASE 5. CASE OF ABDOMINAL INFECTION WITH MEDIASTINAL AND PLEURAL TUBERCULOSIS AND RELATIVELY LITTLE PULMONARY INVOLVEMENT

taken up for growth purposes and might be deposited at irritated areas, or where there is high acid concentration.

4: Relation of Lymph-Node and Parenchymal Lesions: Because of the rapid spread of infection in the lower animals, this relationship is usually difficult to follow. In the monkeys there was never a parenchymatous without a lymphatic lesion. In the four cases in which older focal areas were found, the lymphatic process was greater on the corresponding side. In two carnivores adequately described in protocols, the lower mediasti-

nal rather than the higher tracheobronchial lymph nodes were affected. The data do not permit a statement that lymph nodes were more or less affected with apical or disseminated processes, but the writer is satisfied that his experience would justify the statement that the more distributed the process within the lung, the greater the lymph-nodal involvment. The reverse is, however, not the case for there can be large caseous



8676 Rhesus Macaque ♀ (Macacus rhesus)

This monkey was received in the Garden during August 1926. It gave a bad chart after each of three tuberculin tests and was killed April 14, 1927. All processes active. The entire R. lung was tuberculous with peribronchial and pneumonic cavitation. Bronchiectasis at "x". There was also a tuberculous nodule in the liver.

The areas marked "1" in the left lung are chiefly young, active, degenerating tubercles. There are, however, in two areas, older fibrous tubercles that are retrogressing. They seem to be beside terminal bronchioles or perhaps in the adjacent septum. It can be stated certainly that these are not very old, but are probably retrogressive tubercles of the same age as the infection that caused the massive involvement of the middle lobe and right lung. There is no calcification.

1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary
a. Small spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading.

FIG. 6. CASE 6. TO ILLUSTRATE A CHRONIC AEROGENIC INFECTION WITH FIBROUS FOCI IN LEFT LOWER LOBE

lymph nodes without discoverable parenchymatous foci. This is especially well shown in domestic cows.

5: The Relative Position of Retrogressive Lesions to Active Lesions: For this purpose special attention was given to cases 1, 2, 4 and 7 that showed older focal lesions. In every case these were in close relationship to the acute or progressive processes. This would suggest but not prove the awakening of a dormant focus. In so far as the exact locality

of the oldest fibrous scar-like lesions were concerned, they were found 6 times in the cephalic lobe and 6 times in the caudal lobes. But this may be misleading, for the 6 cases with cephalic involvement showed nine spots, whereas the 6 caudal cases had 13 spots. The caudal lobes are more often the seat of settlement of bacilli, especially in animals infected by the alimentary tract, and this may be the case in the above instances.

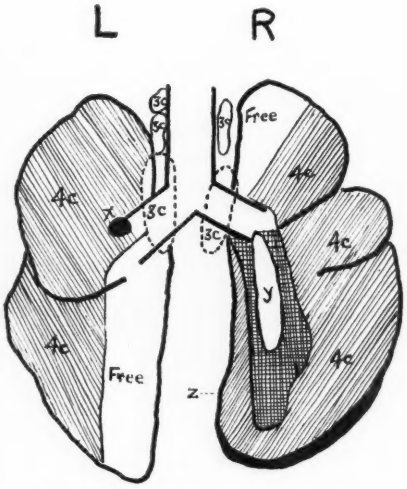
FIG. 6A. CASE 6. ROENTGENOGRAPH OF THIS LUNG. THE BRONCHIECTASIS AND FIBROUS AREAS CAN BE DETECTED EASILY. THIS PHOTOGRAPH IS REVERSED FROM THE DRAWING

6: Alimentary versus Respiratory Infection: Our already published figures[4] would indicate that these two routes are about equivalent in the wild animal. We may demonstrate by the use of figures 2, 3, 5 and 6 that alimentary-tract infection is more definitely lymphatic and pleuro-mediastinal, while aerogenic infection enters the parenchyma of the lungs.

[4] ***Disease in** Captive Wild Mammals and Birds*, Lippincott, 1923, 486.

Figures 2 and 6 are cases of animals almost certainly infected *via* the respiratory tract and show advancing parenchymatous lesions. Cases shown in figures 3 and 5 had very definite abdominal foci of considerable age and presented extensive lymphatic and pleural involvement with relatively little replacement of respiratory tissue.

7: Pulmonary Disease when the Portal is elsewhere and when it is certainly in the Respiratory Tract: This subject is partly answered by the



8681 Vervet Monkey ♂ (Cercopithecus lalandii)

This monkey came to the Garden in January 1927 and passed the tuberculin test; but because he had been associated with a tuberculous monkey, was held in quarantine. Retested two months later, he gave a positive reaction and died one week later. Autopsy showed rapidly advancing acute lesions. No attempt at healing.

Description of lung.

x - Firm, fibrocaseous area lying on bronchus.

y - Bronchiectasis of descending branch.

z - Older fibrocaseous area surrounding bronchus.

Diagonally shaded areas thickly beset with early caseous tubercles and infiltration.
Lesions in bronchial and tracheal nodes seem oldest. No calcification.
Entire pleural diaphragmatic region adherent.

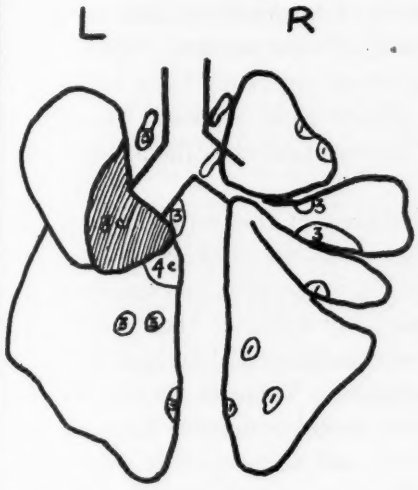
1. Fibrous scar
2. Calcific focus
3. Caseation
4. Fibrous, ulcerative, degenerative or miliary

a. Small scar
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading

FIG. 7. CASE 7. SHOWING OLD FOCUS ON LEFT BRONCHUS, PROBABLY A LYMPH NODE, AS ALL THE OTHER LYMPH BODIES ARE INVOLVED. THIS COULD BE THE FOCUS FOR DISSEMINATION

foregoing heading. Studied from the standpoint of disposition of major lesions, the matter appears somewhat clearer. Among the 38 animals recently studied, 15 had active tuberculosis, and of this number 9 had lesions that, by all the criteria we could use, were of respiratory origin. Of these 9, five had no gross lesions in the abdomen, and 2 had moderate

lesions in the spleen or liver or both. One had a large mesenteric mass and one had a small intestinal mass. This, taken with the data in heading 6, would seem to support Scott's contention of the prominence of pulmonary lesions in aerogenic infection and their inconspicuousness in alimentary infection.



8230 Black-footed Cebus ♂ (Cebus apiculatus)

This monkey was one of three of this variety included in a shipment received direct from South America in September 1925, as a gift from a member of the Zoological Society. It was rejected on each of two tuberculin tests, and killed March 30, 1926 because of poor condition. The liver and spleen were found tuberculous as well as the left lung. The two companions who had shared the cage with him on the trip are still living and apparently in good condition.

The areas marked "1" probably correspond to small, diffuse, interstitial, fibrous tissue increases with constriction of the alveoli, like a fibroid pneumonia. There are no areas of calcification. All areas marked "1" measure about 2 mm.

1. Fibrous Scar
2. Calcific focus
3. Caseation
4. Fibrous, Ulcerative, Degenerative or Miliary

a. Small Spot
b. Limited to 5 mm.
c. Above 5 mm., diffuse or spreading

FIG. 8. CASE 8. FOCAL LESIONS IN THE LEFT BRONCHIAL REGION WITH RECENT LOCAL EXTENSION. SCATTERED FIBROUS LESIONS ARE NOT OF TUBERCULOUS HISTOLOGY

ORDINATE TUBERCULOSIS IN VIEW OF THE THEORIES OF VON BEHRING AND OF OPIE

The writer is aware that the extent of material closely studied in recent months is hardly great enough to justify conclusions in this direction, but ventures to presume that these observations with the records of the laboratory may afford some ground for thought and further investigation. The first difficulty that is encountered is in the difference between youthful and adult human tuberculosis and the similarity of the disease in all

the specimens of wild animals at our command. Too seldom do we know the age of a specimen and we are compelled to note it as young, mature or old. None the less, the lesions are certainly not enough different in young and old monkeys to have caused discussion of it in the literature. That there is a gradation from very rapid to very slow fatal infection is certainly the case, but this might be, and indeed is known to be, due to the presence or absence of concomitant disease of other kinds, to injury, to uncongenial mates and other reasons. Realizing the limitations of the argument, the different orders are to be taken up separately since they exhibit differing pathological responses. Only those orders are discussed that have had representatives in the autopsy material of recent months.

Primates: Tuberculosis in the lower branches of this order appears most in apes and African monkeys, less in new-world monkeys and not at all in marmosets, in our experience. It is a progressive process, with little tendency to focalization and without any evidence that calcific nodules are to be formed. Because of these characters and rapid course, it fits in with both theories under discussion. There is no chronic ulcerative phthisis, which, according to Opie, would occur only if calcific deposits were present. It is both aerogenic and alimentary in origin, but, because the pulmonary parenchyma is most involved when the aerogenic route is followed, less support is found for von Behring's alimentary theory. Tuberculosis in the *Primate*, therefore, seems to be explained as a recent direct pulmonary or alimentary infection, and its morbid characters support the theory of Opie.

During the last twenty-two years every monkey in our collection has been tested with tuberculin and found negative before admission to the general collection. Certain apparently "husky" specimens with suspicious reactions have been put in an outside bandstand cage, where several have lived for many years. Some have died and some have interesting histories that are appended.

7201: Rhesus Macaque, no. 197, ♂. Born May 23, 1923. Parents unknown. Osteitis deformans of mixed type; hypertrophy with irregularities of epiphyses. No sign of tuberculosis; no gross scars in lungs. Born in and never left bandstand.

3863: Rhesus Macaque, no. 147, ♀. Received July 10, 1911. Tested 6 times in 4 years, never giving a wholly unexceptionable chart, but passed to bandstand after second test with other not wholly satisfactory monkeys. Returned

two months later, held and tested twice, being passed after three months at laboratory quarantine. Sent to the monkey house because this chart was her best. Unwise. Put in bandstand 4 months later; had a baby the following year (1914); both put in monkey house, where they remained about 1 year. Not in good condition; sent to laboratory April, 1915; did not pass test; put into open cage by lake. To the laboratory again in October, 1915; did not pass; lake cage again. Died February 4, 1916. Autopsy shows recent active miliary lesions with older lesions in abdomen and in brain. (Figure 4.)

3312: Rhesus Macaque, no. 169, ♀. Received March 17, 1914. Gave good temperature chart. Passed to bandstand, where she was exposed for a short time to 3863. Because others abused it, put in separate lake cage August 5, with Rhesus no. 156. Died September 20, 1914. (Rhesus no. 156 died 2 months later; no tuberculosis.) Monkey tuberculosis of ordinary type, but not very extensive. Most prominent lesions are fibrocaseous and pyoid mediastinal mass and caseous cerebral mass.

4275: Rhesus Macaque, ♂. Received June 3, 1911. Gave two good charts. Bandstand 6 years. Death from infected wounds. No signs of tuberculosis. Parasitic cysts under pleura. Much lymphatic anthracosis.

3121: Rhesus Macaque, ♀. Received April 10, 1913. Died January 25, 1914. Adult. Passed good test. Bandstand only. Autopsy shows some fibrosis about bronchi, with dilatation and circumferential fibrosis (hyaline) which all appears like a congenital bronchiectasis. (From notes it seems that these lungs were thoroughly cut and no scars found.) Animal had amoebic dysentery.

3138: Rhesus Macaque, no. 139, ♂. Received June 3, 1911. Died February 13, 1914. Several tests, most of which were not satisfactory. Exposed to Weeper Cebus no. 55; retested and was suspected, but put into bandstand. After 2 tests, over a year, passed to monkey house where he died of colitis, possibly amoebic. Lungs only fairly well studied; probably no tuberculosis scars; cyst-like areas with congestion, possibly parasitic.

Of these histories that of 3863 is most significant in showing that, despite living four years after a suspicious reaction, most of the time out of doors, infection was slowly progressive and never healed, although it may have been latent for a time. Its young was not thoroughly sectioned, but gave no gross tuberculous lesions. The remaining five animals gave suspicious charts, perhaps because of osseous or intestinal nontuberculous disease, but were without focal calcification or focal lesions to account for their freedom from active disease.

Carnivora: This order has pulmonary lesions that resemble most closely those of human phthisis. The distribution of the pulmonary lesions is, however, different in that the caudal lobes are definitely more affected than are the cephalic. Lymphatic-drainage areas do not show caseous masses with the regularity of human youth. Calcification is not a characteristic of either a limited caseous mass or isolated foci within the parenchyma. There are few gradations of infection from latent to active, all of them appearing slowly progressive. Whether these animals are infected in youth or adult life can be only surmised. Respiratory lesions are the rule and lymphatic lesions inconspicuous. These animals are not especially gregarious, do not nose each other very much, but swallow whole or nearly so all they eat, and lick their surroundings. General evidence would suggest that they get the pulmonary infection *via* the alimentary tract, allow the bacilli to pass through the lymphatic system, and settle in a place of vantage and produce a chronic process. Abdominal tuberculosis occurs, but is rare. There is no evidence that infection in youth and recovery therefrom lays a foundation for chronic ulcerative disease.

Ungulata: The fibrocalcareocaseous lesions of this order bespeak a very definite type of reaction. Evidence from all quarters credits the respiratory tract with the major rôle in the origin of infection, yet lymphatic tissue in these beasts is not only a filter, but a seat of very definite and characteristic lesions. This is likewise true of the serous membranes. Evidence that there are separated, healed, calcific foci is not to be found in 7 examples of recent study, in 19 tuberculous cattle recently autopsied, nor in our records. In our protocols lymphatic lesions outnumbered parenchymatous, and most of them were frankly caseous. These data would not favor the origin of adult tuberculosis as a reinfection, but rather as a slow process in an animal of peculiar receptivity.

Marsupialia: The two cases of tuberculosis in this order exhibited lesions in the abdomen, the lungs being free. Emphasis can be placed only on the obvious alimentary origin, the freedom from active lesions of the lungs, the scarcity of the disease in marsupials, and the fact that both these animals were presented from private sources.

SUMMARY AND CONCLUSIONS

Conclusions from these data upon this as yet controversial point seem unnecessary and perhaps unwise. One might with propriety state that

both theories as to the date of origin of tuberculosis find support in some animal's response to infection. Certainly the exact homologue of the history and anatomical development of tuberculosis in man is not found among the lower animals, so that great caution must be used in deducing from animal experimentation how the human disease arises. On the other hand there is a strong similarity between tuberculosis in wild and in domestic *Ungulata*. On the whole, it seems best to consider that each order of animal exhibits a receptivity as a peculiarity,—behaviorism as the modern vogue would put it.

And this last thought may act as a summary of the text of this paper,—ordinate receptivity or susceptibility is a very distinct feature of the disease tuberculosis. But one may with propriety go more deeply and show that zoological family receptivity is likewise important, perhaps more important than is ordinate. It is certainly true that some families of *Primates* are more susceptible than others, and this is also true in the families of the orders *Carnivora* and *Rodentia*. *Ungulata*, to which the domestic cow belongs, show the same type of morbid lesions in all the families that have come to our attention, and we believe that all families are about equally susceptible, even though some, *Tapiridae* for example, have not shown the disease at our laboratory. The lesson to be drawn from these data is that lower animals behave in a definite manner when they meet the tubercle bacillus for the first time. There is no true healing, as occurs in man. Certain varieties of animals, the kangaroos for example, seem to have no receptivity for the bacillus.

Is the response of man due to a peculiar natural form of receptivity and resistance, is it an inheritance because the disease has been in the human race many centuries, or is it because the human child meets the germ early in life and, if he overcome the attack, acquires a resistance? In the face of the facts that have been adduced here, the thought that the human being reacts in a peculiar characteristic manner because he has a definite type of reactivity cannot be dismissed until we explain why the domestic and wild bovine react identically, the *Carnivora* react like adult human beings, and why certain *Primates* react like youthful human beings, and other *Primates* do not react at all. It seems, therefore, that individual peculiarity of an order, family or genus must play a very large rôle in the inception, development and result of tuberculous infection. Infection early in life and a recovery therefrom will not explain chronic ulcerative tuberculosis in carnivores, chronic calcareocaseous lesions in

bovines, nor will it satisfactorily settle variations in disposition in families of the same order. The types of disease are so peculiar to animal groups that the awakening of latent youthful infection according to the von Behring theory will not explain all the characteristics. Therefore it would seem that human phthisis is a specific type of receptivity for the bacillus and not the result of acquired immunity, that the calcareo-caseous morbid anatomy of bovines is peculiar to them, and so on through the groups.

These data would also strongly support the thought that infection may occur at any age and that the hygiene of animals must guard adults as well as young.

FACTORS FUNDAMENTAL TO HEALING IN TUBERCULOSIS[1]

F. M. POTTENGER

If one desires to understand how healing is brought about in tuberculosis, he must familiarize himself with the immunity reactions which accompany the disease. The key to the understanding of healing is an appreciation of the fundamental difference between primary infection and reinfection, and the difference in the body's reaction toward these processes. Every measure which is of value in the cure of chronic tuberculosis, that is, tuberculosis due to reinfection, must either increase and build up the competency of the patient's immunity mechanism, or stimulate those natural factors in his defensive mechanism which favor healing. All measures which improve the general physiological equilibrium in the body, such as a carefully adapted regimen of rest and exercise, open air and food, sun, air and water baths, pulmonary compression and surgical measures, the relief of symptoms and complications, and the development and maintenance of a proper psychological attitude are of value to the extent that they aid the patient in developing a competent defense, and in maintaining physiological balance.

HEALING OF PRIMARY TUBERCLE

We assume that most people living in civilized countries harbor sufficient bacilli within their bodies at some time during their lives to produce a tuberculous focus. We assume further that an adult will withstand a much larger dose of bacilli than a child without infection taking place, and also that he will be able to overcome a more extensive lesion when once established. Statistical data show the greater acuteness of the process in those infected in infancy as compared with those infected in later childhood and bear out this assumption.

When bacilli gain access to the tissues for the first time, they are immediately opposed by the body cells. The fixed cells proliferate, forming the epithelioid cells; and leucocytes gather in larger numbers. These

[1] Read before the Post Graduate Assembly of North America, Kansas City, Missouri, October 21–27, 1927.

envelop the bacilli, forming the tubercle. At first this is largely a noninflammatory reaction. It is nature's nonspecific way of attempting to hold the bacilli in check at the point where they first enter the tissues and to prevent their spread. Many of the bacilli are engulfed and destroyed; others extend almost immediately to the neighboring lymph nodes, which react by repeating the same sequence of events which occurred at the point of inoculation. Regardless of the barriers placed in the way by the local tissues and the lymphatic structures some bacilli gain entrance to the blood-stream, and circulate until they either are destroyed or are screened out in some such structure as a bone, a joint, or the meninges, there to start a local lesion. Bacilli causing infection in any organ or structure prior to the time when allergy has been established do so without calling out inflammatory response.

For the most part, the struggle for existence on the part of the bacilli is successfully maintained only at the primary point of inoculation and in the regional lymph nodes which receive drainage from the primarily infected area. Only occasionally do circulating bacilli produce infection in some other organ. This first part of the struggle is nonspecific. It resembles the manner in which the body attempts to render innocuous any kind of particulate matter which enters the tissues. But soon the body's defense passes into a second stage. As a result of the growth and death of bacilli, substances are liberated from this focus of infection which pass into the body fluids and, circulating through the tissues, make the body cells throughout hypersensitive toward tubercle bacilli and tuberculoprotein. Thereafter the reaction of the body cells toward bacilli and bacillary protein changes, and, if infection takes place, inflammation and exudation dominate the process and the resulting tuberculosis becomes a different disease. It assumes a chronic character, and the body's defense becomes a specific matter.

Experimentally, evidence of specific defense as manifested by tuberculin sensitiveness of the skin shows in about five or six days after infection with large numbers of bacilli and in about three weeks after infection with few bacilli. We assume that much the same time relationship holds in human beings. While specific defense has no part in combating primary foci immediately after infection occurs, it becomes an important factor after cell hypersensitiveness has been established. From the time that immunity has begun to be established in primary infection this cell hypersensitivity constitutes a factor in altering reinfections and in determining the course that they shall take. A reinfection in experimental tuberculosis produced any time after four or five weeks from the time

that the primary infection took place acts upon the immunizing mechanism already called into play, and changes the entire process into one of a chronic nature. Cell hypersensitivity promotes an increase in reticulum and aids its conversion into collagenous fibres and scar, and so becomes an important factor in promoting healing.

A primary infection is essentially an acute disease. The healing of primary tubercle is usually accomplished through calcification. The probable reason why healing so often occurs is because the infection is produced by relatively few bacilli; so few that the nonspecific defensive forces of the body are able to overcome the bacilli or hold them at bay until the specific immunizing mechanism of the host has been brought into successful play. When large numbers of bacilli make up the primary inoculation, whether it be in a child or an adult, death will nearly always ensue as a result of acute tuberculosis.

HEALING OF REINFECTIONS

The reaction of the body toward reinfection is fundamentally different from that toward primary infection. Whereas primary infection takes place in a nonimmunized and a nonsensitized individual, reinfection at once plays upon the individual's specific immunizing mechanism, which has already been set into motion, stimulating and increasing it; and, even though the numbers of bacilli causing the reinfection may be so large that the individual may eventually succumb to the disease, this will not occur until the disease has assumed a chronic instead of an acute course. In this connection it is the common experience in experimental tuberculosis that a tuberculous animal which receives a second infection lives about twice as long as the one which does not. It is only reinfection produced by very large doses of bacilli, so large as greatly to depress the host's defensive powers, that shortens the course of the disease and produces early death.

Reinfections prolong life, first, by increasing the immunity which already has been established by previous infection; second, by stimulating the allergic response of the body cells and creating a barrier against the ready spread of the invaders; and, third, by producing reaction favorable to healing in and about previously existing foci.

The tubercle, which we have long held pathologically as almost specific of tuberculosis, we are now learning is not a *sine qua non* for the tissue reaction to reinfection with Koch's bacillus. Here inflammation and exudation, expressive of the allergic state of the tissues, are the pro-

nounced pathological reactions, and tubercle-formation is a less constant effect. Bacilli may lie in the tissues even without provoking tubercle formation.

The essential difference between primary infection and reinfection is that the first infection takes place in virgin soil, in tissues which have never before come in contact with bacilli or bacillary protein in such a manner as to find it necessary to develop a specific defense against them, and is combated only by the natural defense of the host; while later infections, on the other hand, occur in tissues already sensitized to tubercle bacilli and are combated by a specific immunizing mechanism, which has been established by previous infections. Reinfections produce chronic tuberculosis. When we think of the cure of tuberculosis we are thinking either of a limited primary infection caused by a few bacilli, or of a chronic tuberculosis. When we think of chronic tuberculosis we are thinking in terms of tissue resistance or immunity.

NATURE OF IMMUNITY AND CURE

Whether or not a given patient shall overcome his particular infection depends upon the competence of his immunity reactions at the time when called upon. In order to cure the infection there must be ample protection against spread by reinfection and adequate tissue reaction to bring about healing of existing foci. Immunity in tuberculosis is relative, varying in different individuals and in the same individual under different conditions and stresses of life.

Tuberculosis has its own particular problems of cure, which are especially bound up in the nature of the bacillus,—its slow growth and its resistance to attack by the body's protective elements,—hence the difficulties encountered by the host in its destruction. Because of the waxy envelope surrounding it the bacillus becomes a foreign body on entering the tissues, and is hemmed in at once in primary infection by the proliferating fixed cells and leucocytes which surround it, forming the tubercle, and by inflammatory reaction in reinfections. Furthermore, because of this waxy envelope which protects the bacilli from the action of the body fluids, their destruction and elimination becomes more of a cellular than humoral affair.

Protection of the host against infection has two phases: one consists of certain phenomena which occur at and near existing foci; the other, of those which occur throughout the body. Some are nonspecific; others specific.

Those phenomena which occur at and near the focus are tubercle-formation and the focal allergic inflammatory reaction. The latter is called into play whenever bacilli spread to new tissue. It is not confined to the site of inoculation, however, but may affect any unhealed focus found in the body. The reactions vary in degree and may be anything from a slight hyperaemia to a marked exudation. They are essential to the healing of chronic tuberculosis. They may bring about healing through destruction of bacilli *in situ* or by caseation and the rupture and elimination of the cheesy masses, or by resolution, or fibrosis. At times the allergic reaction may be followed by necrosis with a loss of tissue. In the presence of conglomerate tubercle severe allergic reactions may be followed by the loss of so much tissue that complete restoration cannot take place.

Caseation and necrosis, however, although usually much dreaded, must not be looked upon as wholly harmful. Caseation is often replaced by fibrosis; and tissue loss is often a conservative process, without which healing could not occur. When the cheesy tubercle softens and discharges its bacillary contents into a bronchus, a real protective service has been rendered the host, the same as when an abscess is incised or ruptures on its own account and discharges its contents on the outside of the body. Such a procedure is even more necessary in tuberculosis than pyogenic infections, because of the difficulty which is encountered by the body fluids and cells in their destruction of tubercle bacilli. Should the bacillary contents of large cheesy tubercles be discharged into the tissues instead of into a bronchus, the instances in which the host would be able to destroy them or render them harmless would be very few. When the bacillary contents of cheesy tubercle are once discharged, however, the tissues are in a state favorable for a regenerative process to take place. This does not mean that caseated foci do not heal without liquefaction and rupture. On the contrary, digestion and absorption of the caseous material may take place, a new growth of reticulum fill the space previously occupied by the caseous material, and scar follow. As long as the tissues contain infection they are subject to focal reaction whenever a reinfection occurs. Through focal reaction reticulum increases, and minor lesions may be brought to healing in a comparatively short time and more severe lesions in a longer time. Some heal before caseation occurs; others afterward, but before liquefaction and rupture take place; and still others after the necrotic contents have been discharged.

The phenomena, distant from the focus of infection, which protect the host from reinfection, are also a part of this same allergic state of the cells. When new implantations of bacilli take place in a host previously infected with tuberculosis, whether in the same organ or in distant organs, they meet cellular resistance, because the hypersensitivity of the cells is universal throughout the body. If the immunity of the patient is high, the allergic reaction of his tissues will be marked and resistance to infection may be so strengthened that reinfection may not result at all. The bacilli may be distroyed by the reacting cells. In case infection does take place, it may prove to be only abortive; and, even should it become well established, the allergic reaction of the cells still may be sufficient to cause it to heal without producing permanent damage.

Probably the majority of reinfections in early clinical tuberculosis or in tuberculosis where limited areas are involved are successfully combated by the phenomena just described; for it is rare to have extensive reinfections take place in early tuberculosis or from limited foci unless the immunity of the host is for the time being depressed by some severe stress. For this reason early limited lesions are much more amenable than advanced lesions to measures directed toward cure. When the lesions become extensive the areas from which bacilli may escape to produce reinfections are much greater and the likelihood of reinfections occurring is multiplied many times; the numbers of bacilli engaged in the reinfection also are greater, causing more extensive involvement and more severe allergic reactions. These result in much larger areas to be healed.

No matter whether the infection is limited or extensive, or slightly or markedly active, the indispensable factor to success in the natural healing of all chronic tuberculosis is the autotuberculin reaction caused by reinoculation. This builds up the patient's immunity and at the same time stimulates foci to healing. It is this property of the body cells to react specifically against bacilli of reinfections on the one hand, and the ability of the reinfection to cause focal reactions in the mother foci on the other hand, which determine the fate of chronic tuberculosis.

CLINICAL PATHOLOGY AND POSTMORTEM PATHOLOGY DIFFER

Clinical observation in tuberculosis has often been at variance with the pathologist's postmortem reports; and where differences have existed it has been natural to assume that the clinician was wrong. Whatever was found at the postmortem was accepted as beyond question. A very

important reason for variance in opinion between the clinician and the pathologist in a case of tuberculosis exists in the time which elapses between the clinical observations and the making of the postmortem records. There is time for a complete change of picture, and this has caused delay in obtaining an adequate idea of the changes which occur in the lung during the course of the disease.

Often, as clinicians, we have followed patients through years of active pulmonary disease and then through years after arrestment has occurred, and have been amazed at the disappearance of what seemed to be gross pathological lesions. Many times, without access to previous records, we would have been confused in locating the site of previous severe lesions. We could not account for this because we had been taught that every tubercle left its scar. We had also been imbued with the idea that healing and fibrosis are almost synonomous. It was only after years of accurate clinical observation and the appreciation of the changes which take place during the course of clinical tuberculosis that the explanation was forthcoming. We now recognize that a great portion of the pathological inflammation which makes up the picture of active tuberculosis is based upon the allergic reaction and is in the nature of a pneumonic exudate, and that this exudate heals by resolution without leaving a scar commensurate with the extent and severity of the process, as may be inferred from the comparison of figures 1A and 1B and 2A and 2B.

Pathologists tell us that tuberculous infections which take place during the stage of sensitization, and this includes nearly all reinfections, cause reactions in the tissues which are the seat of infections that resemble those of caseous pneumonia more than those of tubercle-formation (figures 3A and 3B). Aschoff (1) says: "This caseous pneumonic exudate is composed of fibrin, leucocytes in scant numbers, and above all large cells, so that we speak of a large cell exudate." Miller (2) describes three types of tuberculous pneumonia, depending on the amount and disposition of reticulum in the walls of the alveoli, and in the alveoli themselves, likewise upon the character of the exudate in the alveoli. Jaquerod (3) says resolution in tuberculosis compares in every way with resolution in pneumonia, except in point of time. Pneumonia will undergo resolution in a few days, at most a few weeks; but tuberculosis requires many months.

We appreciate this pneumonic nature of the tuberculous process better now that we begin to understand the inflammatory and exudative nature of the allergic reaction, which forms so great a part of the picture of all

active chronic tuberculous processes. The X-ray has also been a great aid in establishing this fact; but it must be understood that the X-ray does not give a true picture of pathological changes which occur, but only a comparison of the manner in which rays are intercepted by different tissues and by the same tissues under various physical conditions. Nevertheless we often see widespread exudative tuberculous lesions, either with or without cavities, diagnosed by both physical examination and the X-ray, which disappear during healing, leaving little to mark their previous location. While we would probably have been too timorous to have claimed this on physical examination alone, yet with the living every-day changes studied in frequent X-ray plates to back up the records made by physical examination, clinicians now maintain that not only extensive tuberculous lesions (figures 1 and 2A and B) but even cavities will disappear (figures 4A, B and C and 5A and B), leaving the pulmonary tissue at times so comparatively free from pathological change that the site of former lesions may be detected with difficulty or not at all by physical examination or by X-ray. The remnants of the former disease are so slight that they give the pathologist in making an autopsy little or no clue to the severity of the lesion which had been observed by the clinician years before. This opinion is particularly strengthened by the fact that both fibrous tissue and calcium intercept X-rays much more strongly than other pulmonary tissues, and should show on the X-ray plate if healing of widespread lesions had occurred by fibrosis or calcification.

We have long known that tuberculous peritonitis will heal and leave no clue recognizable at the time of future abdominal operations. Tubercles in the eye and miliary tubercles in various organs will literally disappear. All have seen lymph nodes as large as pigeon eggs, or larger, disappear and assume practically normal size. The same thing is true of primary lesions in the lungs and the regional lymph nodes. Testicles will often swell to two or three times their normal size under tuberculous infection and yet return to practically normal size after the lesion has healed. The sites of former infections are not always marked by calcification or by an amount of fibrosis in keeping with the severity of the previous lesions; so we must look for some method of healing to take place other than that of calcification and the building up of fibrous tissue. This we find in healing by resolution.

PROTECTIVE VERSUS REPARATIVE REACTIONS

The reactions of the body against tubercle bacilli, as described in the previous paragraphs, are of two kinds, protective and reparative. The proliferation of the fixed cells, the action of phagocytes, the increase in immune bodies in the blood, the inflammatory reaction of cells to reinfections, the destruction of bacilli, the caseation and rupture of the tubercle with elimination of the mass of bacilli contained therein, are all protective processes. The hyperaemia about existing foci, the exudation of serum and cells which later are digested and carried off or transformed into fibrous tissue, the liquefaction and digestion of caseating masses and the clearing away of the field either before or after cavity has formed, the formation of granulation tissue with its new vessels, the increase in reticulum and its conversion into collagenous tissue, and the deposit of calcium which usually occurs in primary infections and more rarely in reinfections, are all parts of the reparative process.

AUTOTUBERCULIN REACTION AND HEALING

The clinician rarely attempts to carry out a therapeutic program for primary tuberculosis. Either the infection is so severe that a generalized tuberculosis occurs, which results in quick destruction of the patient, or the infection is so slight that it either heals of its own accord or, failing to heal, remains in a state of quiescence, without producing symptoms.

Reinfections, however, are different. The tuberculosis due to reinfection, as before mentioned, is chronic in nature, being a disease which is implanted in immune soil. The term *immunity* in connection with tuberculosis must always be considered as meaning a relative immunity, and as being variable under varying circumstances and stresses of social and economic life and under conditions which accompany diseases.

Koch called attention to the effect of reinoculation with both living and dead bacilli upon the healing of existing tuberculosis in 1890. This has been confirmed by many observers since. It has now come to be common knowledge that even one reinfection will render a previous infection more chronic. The results of many experimenters, agreeing with those of Roemer, Hamburger, and Krause, leave no doubt that repeated reinfections with small doses of bacilli build up a fairly high grade of immunity against infection not only with larger numbers of bacilli of the same strain but also against bacilli of high virulence.

In order to combat clinical tuberculosis successfully every patient must establish an immunity against his own microörganisms, for bacilli

escape from existing foci and attempt to produce reinfections as long as they are not thoroughly encapsulated. Doubtless most of the reinoculations that take place in the regular course of clinical tuberculosis are caused by so few bacilli that they fail to produce permanent infection. The bacilli are destroyed on escaping from the already existing foci or after forming an abortive lesion. Nevertheless, they serve the purpose of acting mildly upon the patient's immunity mechanism and increasing his cell hypersensitivity. Inasmuch as the most marked specific hypersensitiveness is in and around the focus of infection these areas respond to stimulation most readily and probably are influenced by inoculations even of comparatively mild degree. The effect of these reactions is to destroy the bacilli in the tissues and to produce repeated slight stimulation in and around the foci favorable to the laying down of scar-tissue.

Larger inoculations often occur, some so large that severe reinfection follows. The interplay between these and the sensitized cells is most interesting. Oftentimes considerable time will elapse between the time of the reinoculation and the end-result, which may be either a marked lowering of specific defense and a serious spread of the disease or a heightening of immunity and improvement or healing of the disease.

Every reinoculation, successfully withstood, leaves the individual with an increased immunity, and the more serious and extensive the reinoculation withstood the greater the immunity and the greater the healing resulting from it. This is noted both in experimental tuberculosis in animals and in clinical tuberculosis in man. Often the clinical course of tuberculosis is interrupted by a severe spread of the disease. The new infection not only produces an effect at the site of inoculation but also produces an autotuberculin reaction in previously existing foci. This shows on stethoscopic examination of the areas of infection as an increase in signs of activity, the increase in moisture usually being very evident. The X-ray also reveals an increase in those shadows which we interpret as accompanying activity. Clinically, if the reaction is marked, the patient shows an increase in toxic and reflex symptoms. The temperature becomes elevated, the pulse quickens, the cough increases and sputum may double, treble or even increase tenfold. Lack of appetite, loss of weight, malaise, increased nervousness, sleeplessness and general depression are nearly always present to some degree.

This clinical picture may last only a few days and be repeated in from two to three or four weeks or it may be continuous over weeks or months. The important fact is that in spite of reinfections caused by large numbers

of bacilli, even though repeated at frequent intervals and in spite of the exudative allergic inflammation caused by the autotuberculin reactions which accompany them, widespread disease may end in improvement or healing, as shown in comparing figure 1A with 1B and figure 2A with 2B.

Activity in chronic tuberculosis means reinoculation and its accompanying allergic inflammatory reaction, the result of which may be harmful in some areas but favorable in others. This is in harmony with the common clinical observation that healing often goes on in a lung although the disease be active and the temperature high; some areas of infection heal during the same time that others are breaking down. This is well illustrated in figure 3A and B, plates taken one year apart, during which time the patient had continuous temperature ranging from a little over 99° to 103°, and averaging about 100°. Although the left lung continued to break down with cavity formation, the right lung healed.

I have been able to observe this healing effect of the autotuberculin reaction in many instances, and have been able to demonstrate it in X-ray plates and show the effects by unmistakable records which will be published in a future paper.

I have discussed the healing effects of the autotuberculin reaction in several recent papers (4) (5) (6) (7) and will discuss them further in papers which will be published in the near future.

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FIG. 1A. Extensive tuberculous involvement of both lungs, most marked throughout left side and at right a

IB. Plate taken 18 months later, showing disappearance of most of infiltration. Lungs comparatively free.

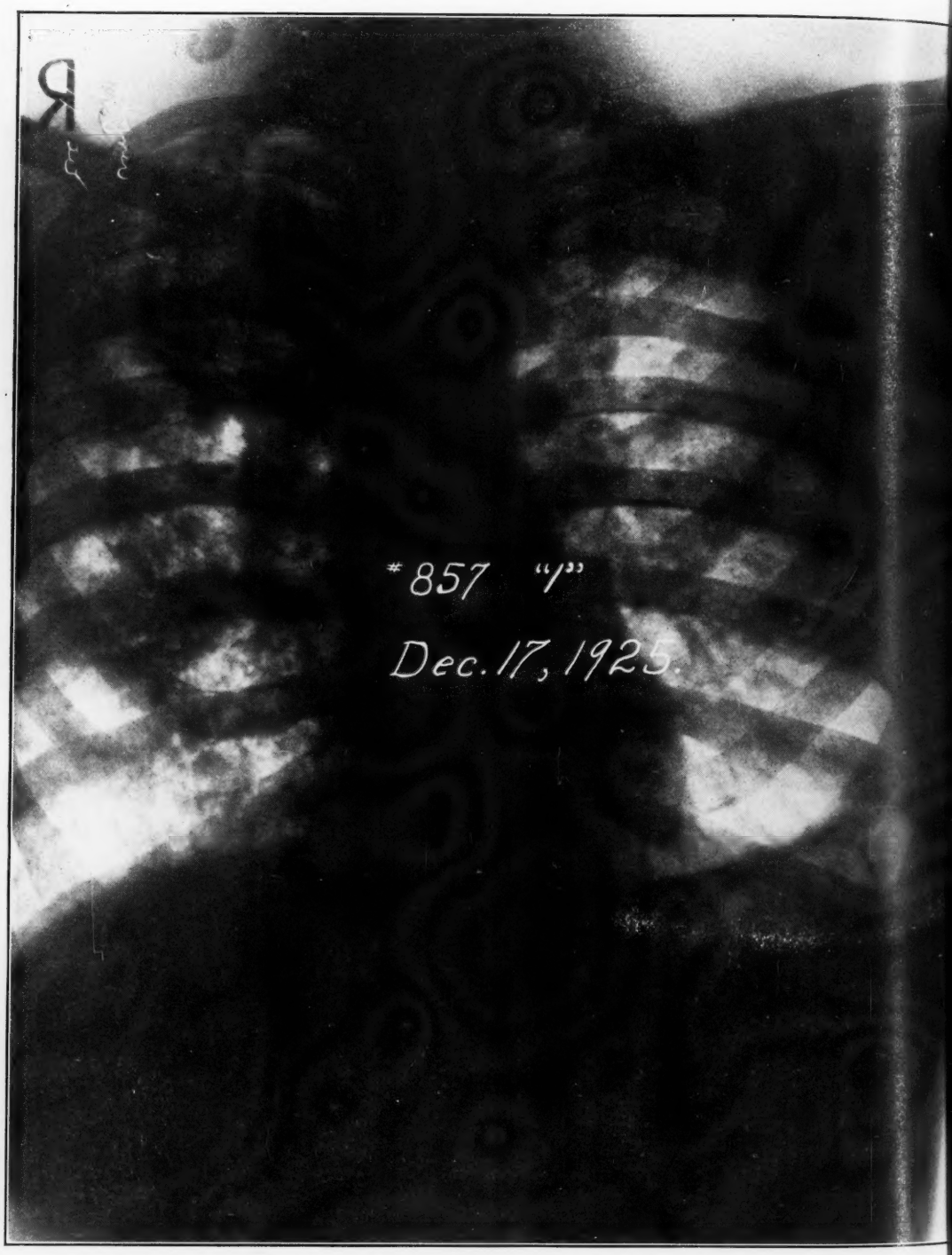
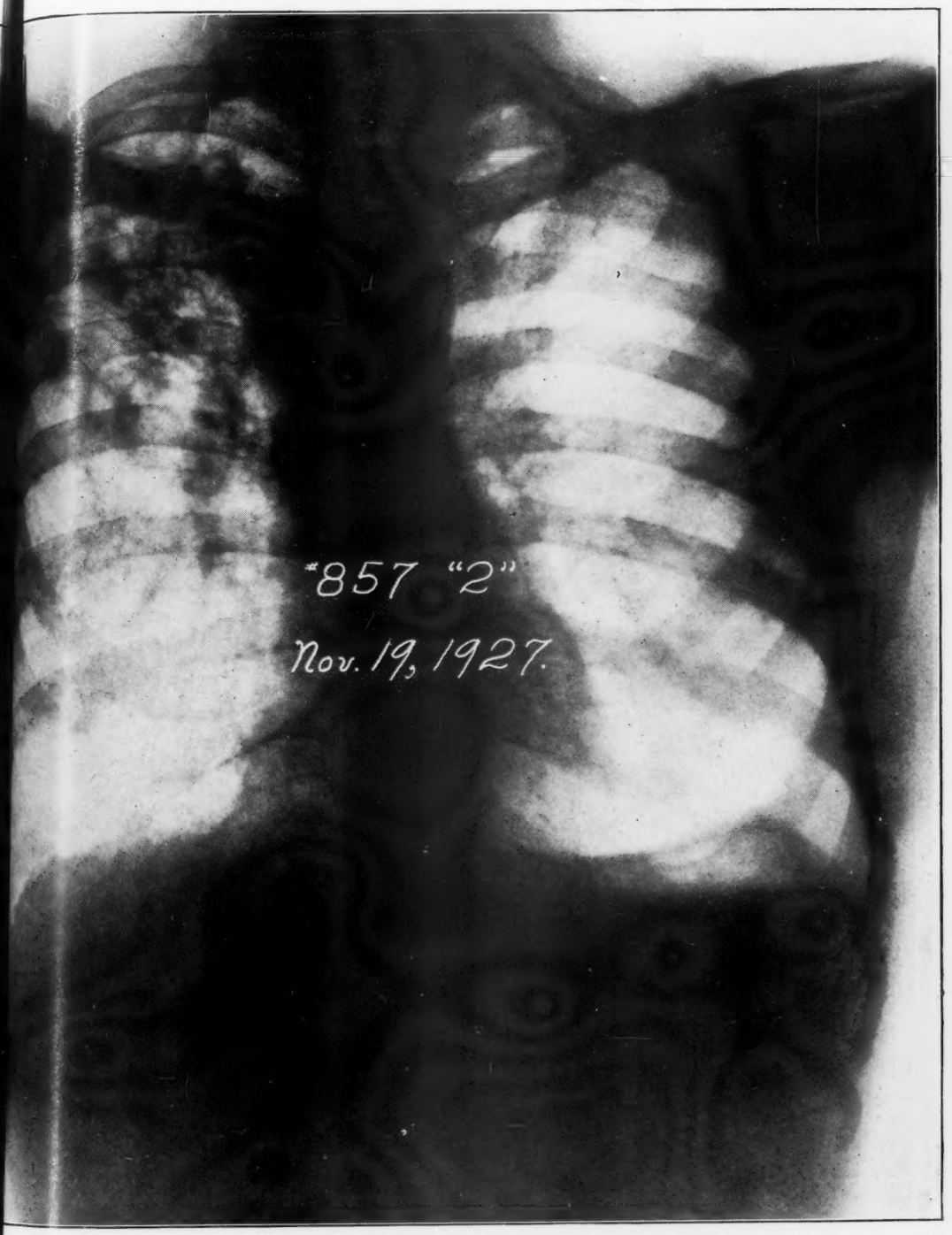


FIG. 2A. Very extensive tuberculous infiltration of exudative type involving both lungs. Infiltration in right lung very dense.



2B. Plate taken 23 months later. Infiltration throughout left lung and lower part of right has largely disappeared, leaving comparatively little scar

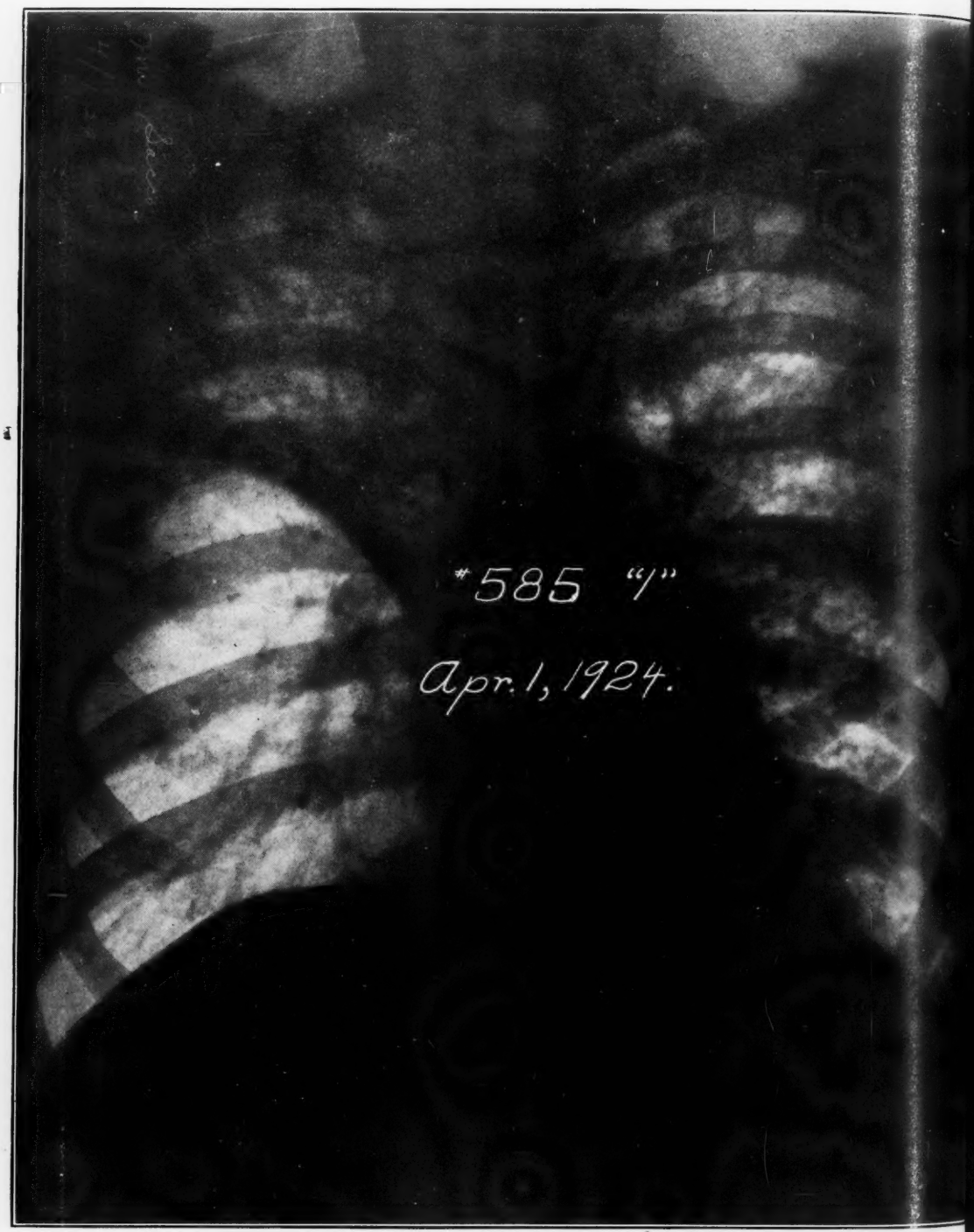
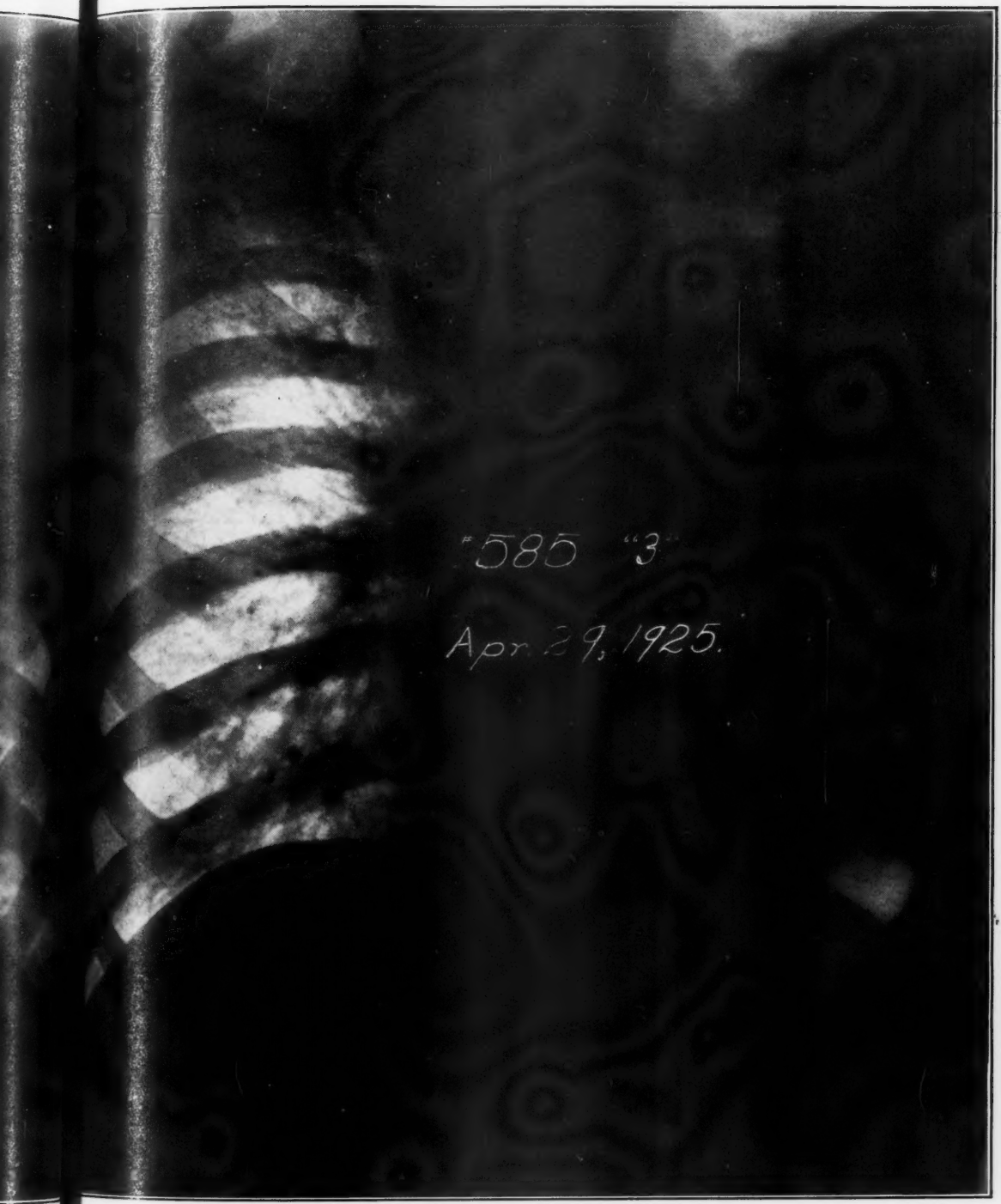


FIG. 3A. Extensive caseopneumonic tuberculosis involving entire left lung, with a lesser infiltration involving upper third of right



upper third

IG. 3B. Plate taken one year later. The caseopneumonic process in the left lung has gone on to the formation of al cavities and is still markedly active. The right lung has almost entirely cleared. The patient has had continuous erature, ranging from 99° to 103° during the entire year. The right lung healed regardless of this process.

FIG. 4A. Patient has considerable infiltration through both lungs with large cavity in upper right

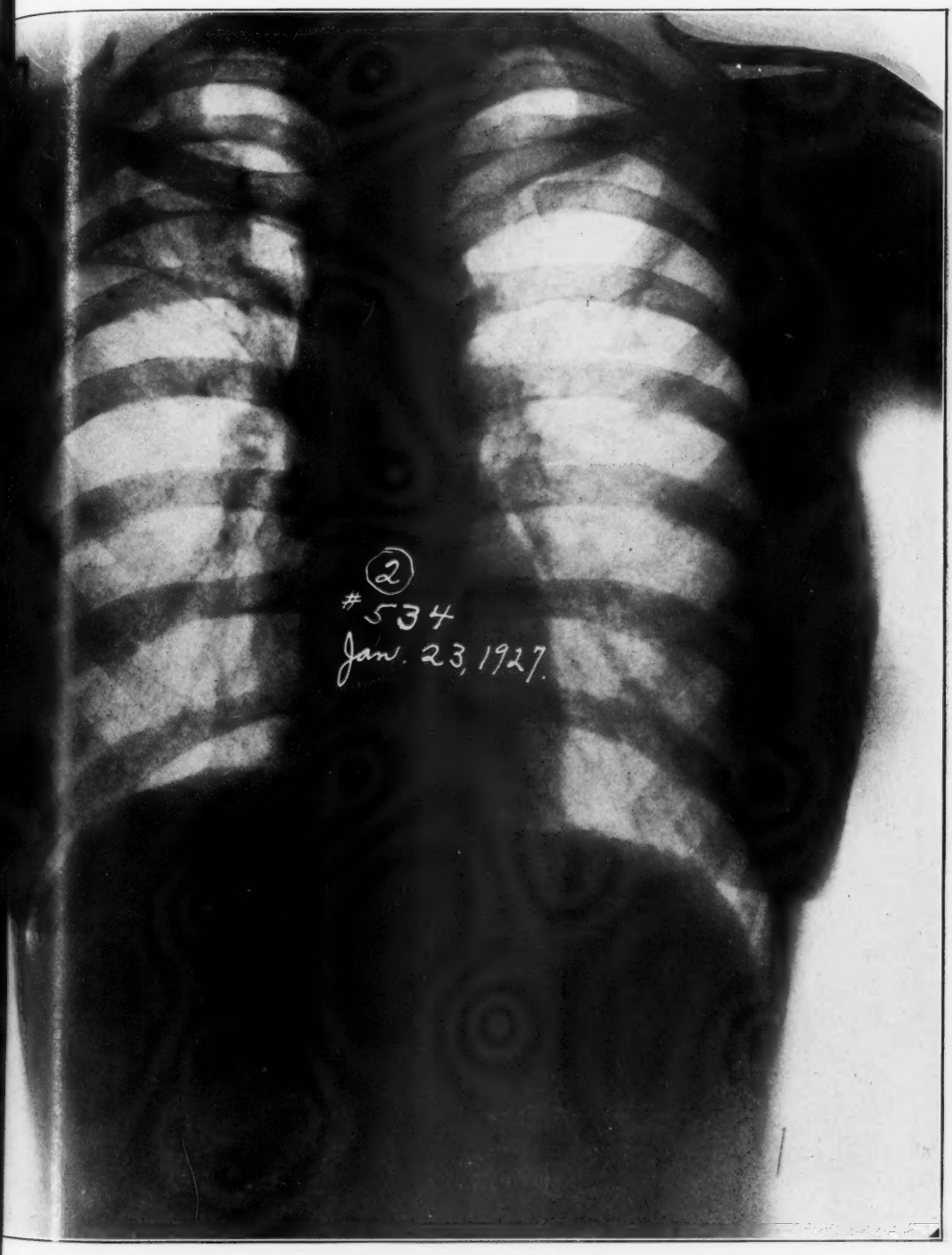


FIG. 4B. Plate taken six months later, showing lung fields clearing and the cavity reduced to about half former size

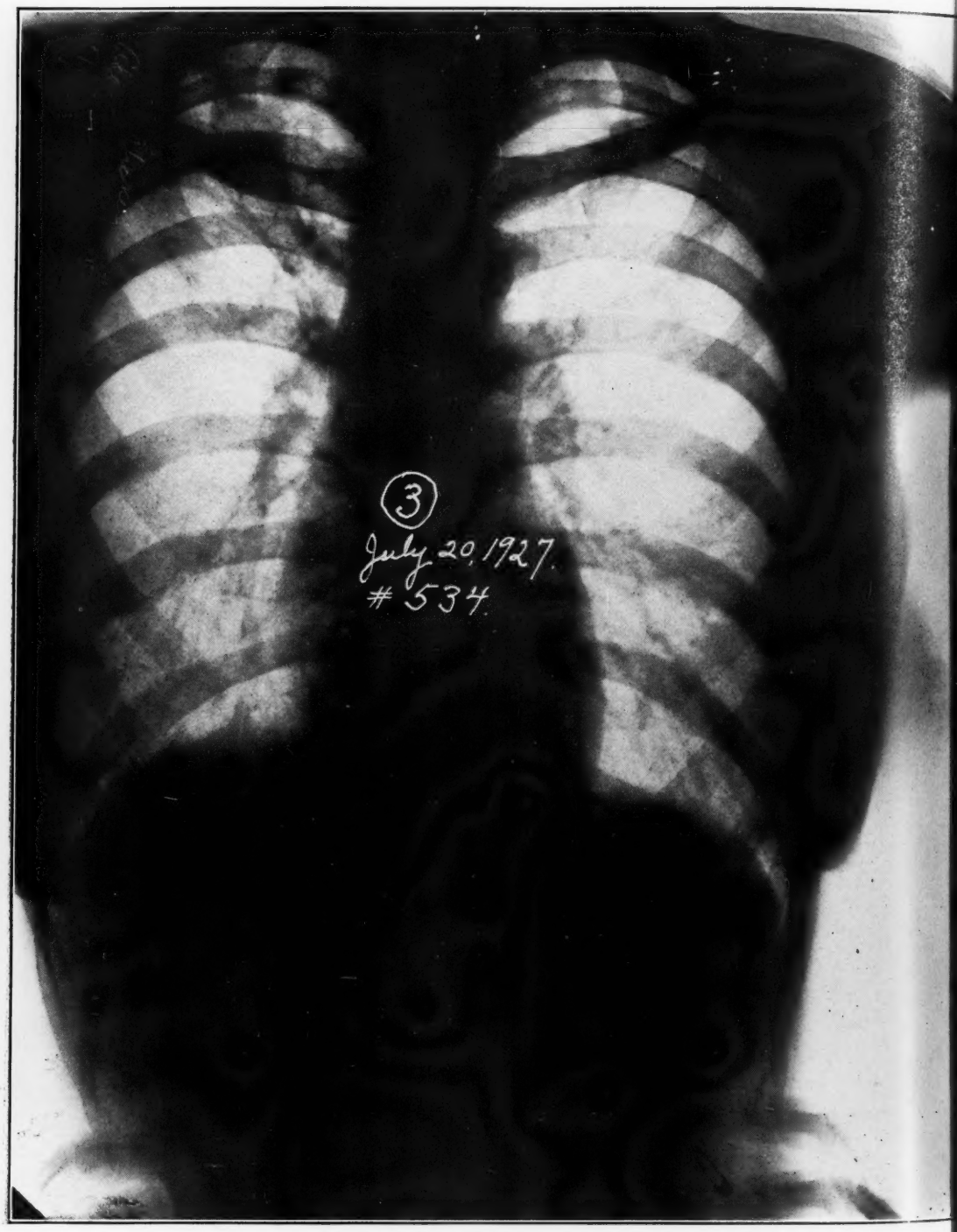


FIG. 4C. Plate taken six months later, showing cavity to have entirely disappeared

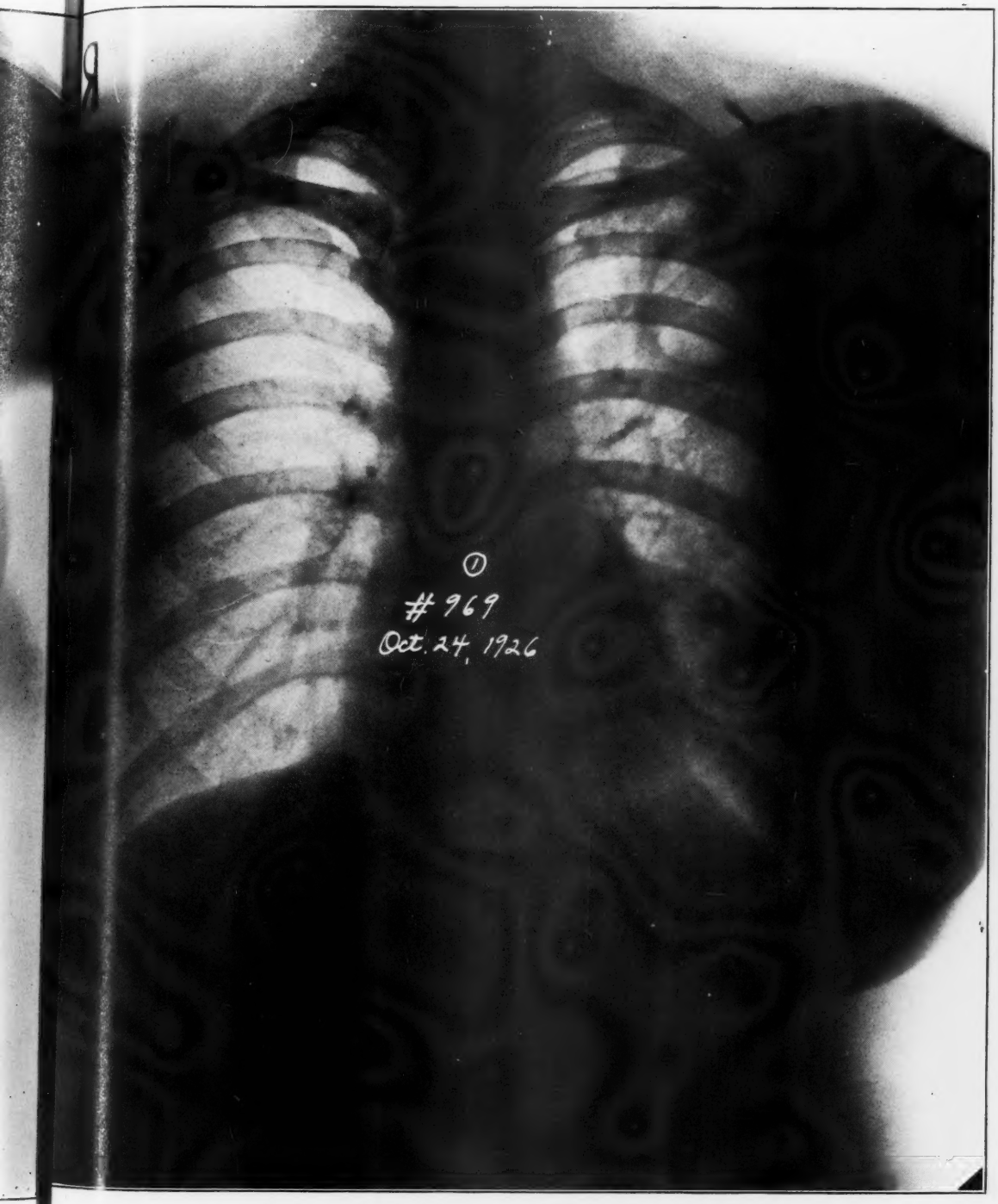


FIG. 5A. Large cavity in upper part of left lung. Moderate infiltration about cavity.

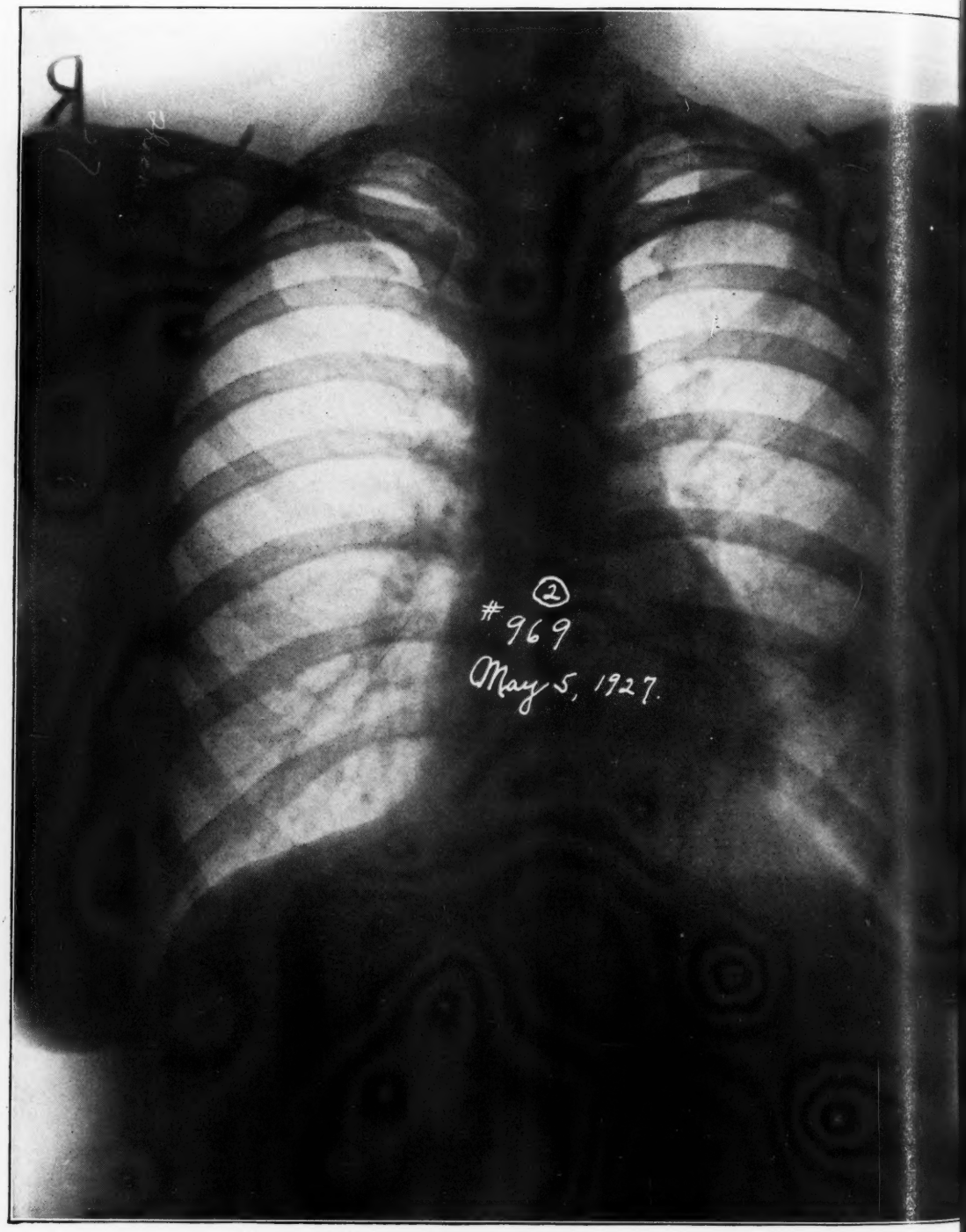


FIG. 5B. Plate taken six months later. Cavity closed.

A HOME-MADE PREPARATION OF IODIZED OIL FOR OPAQUE INJECTIONS OF TUBERCULOUS SINUSES[1,2]

CLARKE BLANCE[3] AND HARVEY R. LIVESAY[4]

This paper intends not only to give the formula and method of injection used by us, but short abstracts of the tuberculosis histories of seven cases are also presented, as they are typical of all of our cases in regard to insidiousness of onset, as well as mistakes made in diagnosing the trouble in the beginning.

The nine figures are likewise typical of all these sinuses injected by us, in that they show large pockets connected by very small tracts through which bismuth or barium will not penetrate.

For well over a year we have been using at Fitzsimons General Hospital the preparation for opaque injections of sinus tracts following tuberculosis of bones and joints. It has been much more efficacious in our hands for diagnostic purposes than the bismuth and barium used formerly.

Cases

1: C. M., male, age 31. Tuberculosis first manifested itself with cervical lymphadenitis in January, 1918. The lymph nodes drained for a few months and then healed. The patient was then well until 1922 when his back became stiff. This was diagnosed as rheumatism and a brace was prescribed. In August, 1924, a swelling appeared over the right iliac crest, which was incised and drained by a physician. It has been draining ever since, and several other sinuses have opened and closed since that time. The patient now has four draining sinuses, one on each side front and back. The focus is in the third and fourth lumbar vertebrae. He must have had an active pulmonary tuberculosis at one time, as both lungs are well fibrosed, although as far as he knows he never had any symptoms of pulmonary tuberculosis.

Figure 1 shows the sinuses injected with 200 cc. of the preparation that just filled them. The three sinuses not used for injection were stopped by an assistant with cotton wads, while the injection was being made and the picture taken.

[1] From the Fitzsimons General Hospital, Denver, Colorado.

[2] Published with permission of the Surgeon General, U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

[3] Major, Medical Corps, U. S. Army.

[4] Captain, Medical Corps, U. S. Army.

2: R. S., male, age 31. The earliest symptom was a stiff back first noticed in June, 1918. The patient began to have pain regularly in December, 1918, and about this time he noticed a swelling in the left lumbar region. He was treated for rheumatism until the cold abscess ruptured spontaneously in 1923 (five years after its appearance). It has never healed.

Figure 2 shows some bismuth that had remained in a pocket for over two years, and illustrates how long bismuth may stay in a sinus tract.

Figure 3 shows the case injected with iodine preparation. There is a very small sinus tract between the larger pocket to the left of the spine and the one below.

FIG. 1. CASE 1

There are four sinuses: one on each side, anteriorly, over the inguinal ligament, and one on each side, posteriorly, over the crest of the ilium

FIG. 2. CASE 2

A pocket of bismuth is seen two years after injection

FIG. 3. CASE 2 AFTER INJECTION WITH IODINE PREPARATION

There is a very small tract between larger pocket to the left of the spine and the one below

FIG. 4. CASE 3

For description see page 484

FIG. 5. CASE 3

For description see page 484

FIG. 6. CASE 4

For description see page 484

FIG. 7. CASE 5

A tract leads directly to the lower portion of the hip joint

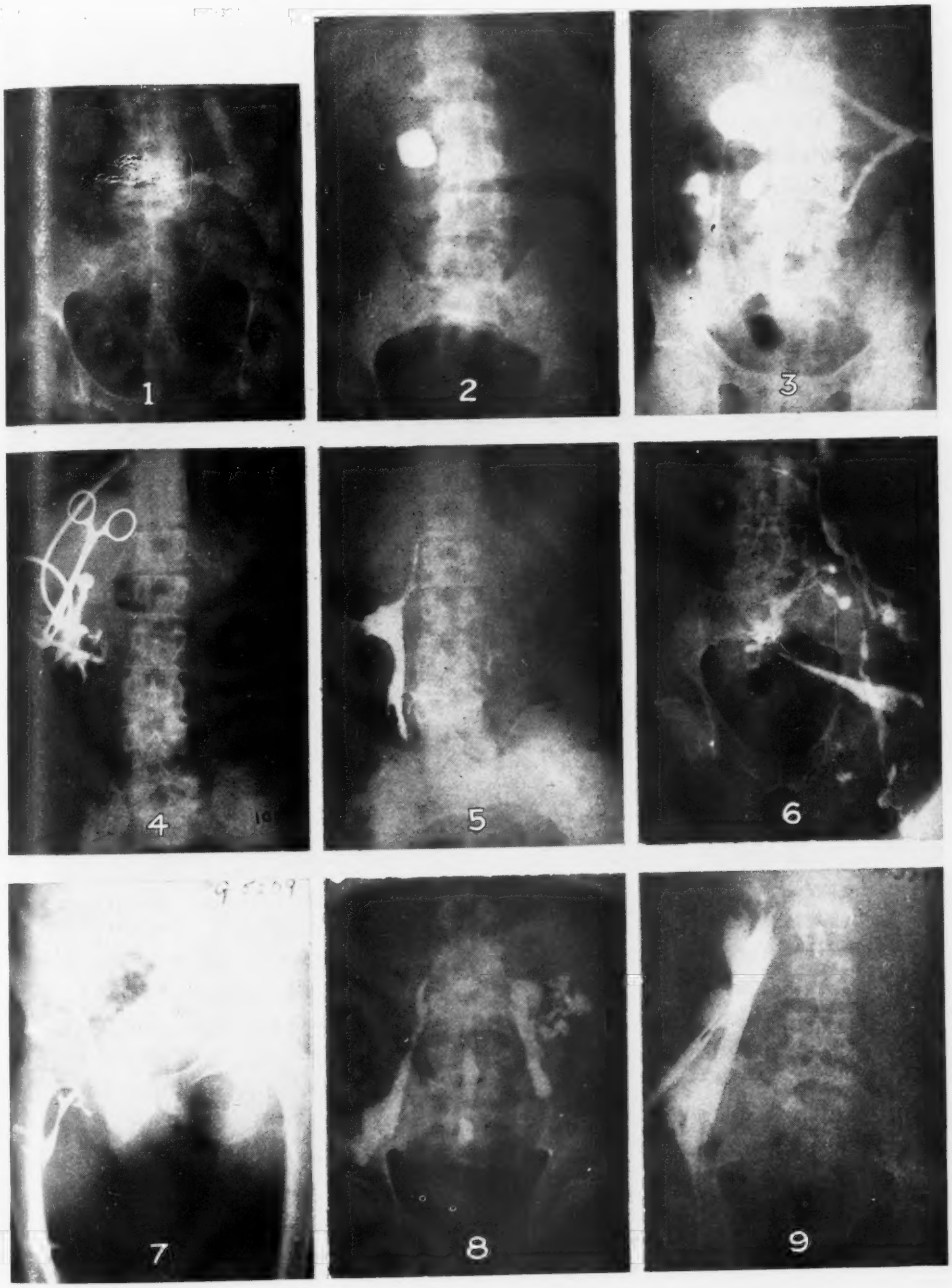
FIG. 8. CASE 6

For description see page 485

FIG. 9. CASE 7

500 cc. of material was used in this injection

Although not shown well in the figure there are very small ramifications through the lumbar vertebrae, and the tract also passes up along the spine to the side and empties into a bronchus through a fistula. The patient has had about 60 cc. of drainage daily through the sinus and about the same amount through the bronchus, and 250 cc. of injection mass was used before he began to cough it up. An exposure made one week after this injection showed no trace of our opaque injections, but the bismuth, as shown in figure 2, was still present. The patient left the hospital against medical advice. He suffered no reaction from the injection.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3: R. W., male, age 30. He had pneumonia in 1921 and pain in the back at that time, when he was in the hospital for 17 months. He had felt fairly well for a year or two, when a swelling appeared in the right lumbar region and was opened for a perinephric abscess. This healed quite readily, but the old scar broke down again in 1926, when a diagnosis of tuberculosis of the spine was made for the first time.

The first illness was probably pulmonary tuberculosis, or at least tuberculosis probably followed by pneumonia, if the patient was sick enough to stay in the hospital for 17 months. His lungs show considerable fibrosis, and in all probability the perinephric abscess was a cold abscess.

Figure 4 shows an abortive attempt at injection with bismuth. The involvement of the third and fourth lumbar vertebrae shows in this picture, but the slight area of involvement of the twelfth dorsal would not be noticed, except for the fact that the upper arm of the sinus tract points it out in figure 5 (an injection with our iodine preparation).

The stereoscopic view shows this injection going through the intervertebral disc between the third and fourth lumbar vertebrae, and a very small pocket can be seen opposite the body of the third lumbar on the opposite side: 90 cc. were used in this case which is still under treatment.

4: T. W., male, age 32. Tuberculosis first appeared as a swelling over the left groin in January, 1922. This was opened and drained by a physician. It healed in a few weeks and remained healed for 9 months, when the swelling again appeared and this time the patient was taken to a hospital to be operated on for appendicitis. At operation they encountered a cold abscess, and a diagnosis was then made of tuberculosis of the spine. There had been stiffness of the back since 1919.

Figure 6 shows the injection of this sinus. The syringe used can be seen in front of the crest of the ilium on the right, and another small sinus was plugged on the internal aspect of the right thigh at about its middle.

In the stereoscopic plates the opaque injection can be seen to extend through the bone and discs for practically the whole length of the lumbar spine. There are also little offshoots into the bodies of several of the vertebrae. Moreover it extends up beside the spine and emptied through a fistula into a bronchus: 100 cc. was used in the injection, when the patient began to cough it up.

We were amazed in this case to see the large size of the tract, for from the appearances of the sinuses and the small amount of drainage we believed the tract to be superficial. (There could not have been more than 2 cc. of drainage from each of the sinuses in 24 hours.)

We were equally surprised when the patient began to cough out our injection, for he had had no symptom of such a condition, that is, no cough or expectoration. He had no reaction from the injection and coughed only a few times. He has left the hospital against medical advice. An exposure

made a few days after this injection showed no traces of the opaque preparation.

5: L. E., male, age 22, had pulmonary tuberculosis since 1921, when too his back began to bother him by being stiff and aching. In 1925 he developed severe pain in the right hip, and shortly afterward an abscess opened spontaneously at the middle of the internal aspect of the right thigh. When admitted to this ward about a year ago the patient had tuberculosis of the lumbar spine and right hip, neither of which had ever been diagnosed. The spine had practically healed, but the hip was active. (Neither of these conditions had ever been diagnosed.)

This sinus (figure 7) held 40 cc., and healed readily under the routine treatment of the hip, heliotherapy and bismuth injections.

6: D. C., male, age 33, had pulmonary tuberculosis in 1918 and some pain in the back at that time. He was up and down until 1926, when a swelling appeared over the right groin and ruptured spontaneously. In the meantime he had consulted many physicians, but no diagnosis had been made until 1926.

Figure 8, of this case, is rather typical of the burrowing of abscesses formed by tuberculosis of the lumbar vertebrae; for instance, it has extended down each iliac fossa and down the curve of the sacrum: 100 cc. was used. The case is still under treatment.

7: Male, age 32, was never sick until he noticed a swelling over Poupart's ligament on the right side. This gradually became larger until the fall of 1923, when it was opened by a physician. It was not drained with tubes, and healed in a few weeks, and gave no further trouble until 1927, when the swelling appeared again. This time the patient was sent to a hospital for a herniotomy, and the surgeon encountered the cold abscess upon making his incision. This was drained with tubes and has remained open to this time.

Figure 9 shows the sinus injected with opaque iodine. A bismuth injection previous to admission disclosed a cavity about half the size of this one, and did not exhibit the fine line running down the thigh to another large pocket which does not appear in this exposure. Over 500 cc. of the preparation was used in this case, and there was no reaction whatever.

The few cases presented above are typical of all of our cases, not only in the physical aspect of the sinuses, that is, many large pockets connected by very small sinus tracts, but they are also typical in that the patients went for years without a diagnosis or at least without the correct diagnosis, and consequently without treatment for the condition that existed. They were likewise typical in the fact that the cold ab-

scesses were operated upon under the mistaken diagnosis of appendicitis, perinephric abscess or hernia, and the few abscesses that escaped any of these diagnoses were either opened and drained intentionally or were allowed to open spontaneously. It is only rarely that these histories reveal any attempt to prevent the cold abscesses from opening by treatment of the basic condition or by aspiration.

In using this preparation for the purpose of outlining the sinus tracts in cases of this nature, it is necessary to inject it under some pressure (two or three pounds), and this pressure should be held for at least five minutes before the picture is taken, so as to give the liquid time to fill all the larger pockets, which at times have to be filled through a very small tract, as is noted in figures 3 and 9. As the pressure is maintained it will be noted that the plunger of the syringe is gradually descending. We maintain the steady pressure for a minute or two after the plunger has apparently ceased to descend. Then we make the exposure, still maintaining the pressure during all exposures.

We use no tubing or catheters, as we find that often there is a pocket opening near the lumen of the sinus that is plugged by the tube. Any kind of syringe is satisfactory for this work if its nozzle fits the opening of the sinus snugly enough to maintain the required pressure without leakage around the syringe. A 30-cc. Luer is satisfactory for most cases. A large needle that has been blunted or the anal tip of a fountain syringe connected to the Luer by a small tube will be found necessary in some of the smaller sinuses, particularly anal sinuses.

Anyone using this preparation in the manner above stated will be greatly surprised by the real extent of the sinus tracts revealed, especially if they have previously been using bismuth or barium. They will obtain information which will enable them to secure adequate dependent drainage (a necessity in cases already secondarily infected). They will also find that a considerable percentage of their sinuses connect with a bronchus, although no symptoms of such a condition are present. Especially will this be true in sinuses caused by dorsal spinal caries.

Out of a series of 30 cases injected on the Heliotherapy Ward at Fitzsimons General Hospital, we found three cases in which the sinus was connected with a bronchus without accompanying symptoms. These three cases all coughed up the solution during the injection. In one case a chest picture revealed it in the tubes, but the others coughed it up too quickly for us to get it recorded on a film. In no case could we trace the exact course after the diaphragm was reached. Our interpretation is that

one end of the perispinal abscess formed in the vicinity of the carious vertebrae has burrowed into a bronchus, while the other end has burrowed down to form the sinus. The shadow cast by these perispinal abscesses is always heavy, and probably obliterates that cast by the opaque injection.

The formula and manner of preparation is as follows:

1. Make a U tube with one end small enough to connect with the rubber tube of a Dakin chlorinating apparatus (a 100-mil volumetric pipette with the upper portion of the bulb removed and the lower end bent is quite satisfactory).

2. Place the U tube in a beaker of cool water and connect the small end to the rubber tube (remove the diffusing tube).

3. Weigh out 20 gm. of resublimed U.S.P. iodine crystals and place in the U-tube bulb.

4. Pass chlorine gas through the crystals until a good many yellow crystals are formed at the upper junction of the iodine and bulb.

5. Remove the U tube from the beaker and wash the iodine chloride into a 2-litre flask with distilled water. The amount of water required is about 100 mils. A little more or less will do no harm.

6. Add 100 mils of Mazola oil (corn oil) to the flask, and shake until a creamy emulsion is formed.

7. Add 100 mils of chloroform to the emulsion, and shake until all the oil is taken up by the chloroform (do not cork tightly).

8. Place in a cylinder large enough to hold the entire lot and allow to stratify.

9. Remove all the watery top solution and all bubbles.

10. Place the chloroform and oil in a large flat porcelain dish over a water-bath and keep the temperature below 70°C., until all chloroform is removed.

The above procedure requires about three hours. The first reaction is a combination of iodine and chlorine, or iodine chloride, part of which is the trichloride. With the addition of water an entirely new combination is formed; that is, hydrochloric acid and hypoiodous acid. When the oil is added the hypoiodous acid combines with the unsaturated oil and the hydrochloric acid is left free. The chloroform simply stratifies the iodized oil, and the weak acid is easily removed. Upon heating, the chloroform is readily evaporated, leaving the concentrated oil with the iodine combined.

One should recover the amount of oil used. This should be neutral in reaction and similar in taste to the pure oil. No free iodine will be

found if properly prepared. Each lot is tested with soluble starch and, if stored in the ice-box, it is retested each time before use for free iodine. The color should be a light brownish-yellow. When exposed to heat and light the color gradually changes to a dark brown; however, no free iodine will appear. It is thought better to store in an ice-box. Before use it must be warmed in a water-bath to body temperature.

Stability of Compound: This preparation is not easily broken down. The strong acids do not liberate free iodine, nor do stomach contents and bile. Subcutaneous and intraperitoneal injections of guinea pigs do not cause any discomfort. In the peritoneal cavity the preparation will slowly change color. A white fatty material appears on the circumference of the mass, and smears from this do not show a true exudate. It apparently is always sterile, probably because of a small amount of chloroform and the material itself.

CONCLUSIONS

1. A new preparation of iodine, described above, will penetrate into very small sinuses where barium or bismuth will not go if thick enough to cast a shadow.
2. It does not stay in the sinuses but drains out readily.
3. It does not block sinuses, and cause burrowing in other directions.
4. Any amount may apparently be used without causing any reaction.
5. It is absolutely nonirritating, and apparently has no effect upon the normal amount of drainage from a wound.
6. It is so cheap that the cost is of no consequence.
7. It is far superior to any material now in use.

NONTUBERCULOUS INTRATHORACIC CONDITIONS

Radiography as an Aid in Their Diagnosis[1,2]

L. R. SANTE

The establishment of the tuberculous nature of a pulmonary lesion changes at once the entire aspect of the case, its prognosis and its treatment. The numerous forms in which tuberculosis manifests itself and the prevalence of the disease make the problem of differentiation one of paramount importance.

In order to differentiate other respiratory infections from tuberculosis, it is necessary to be thoroughly familiar with their X-ray appearances at all stages. I shall direct my attention then to a consideration of nontuberculous diseases of the chest, pointing out as I go along the various phases in which they resemble tuberculosis.

Lobar pneumonia starts as a consolidation in the hilum region, and spreads rapidly to the periphery, involving one or more distinct lobes of the lung. In order to recognize lobar consolidation then, it is necessary to consider the topography of the chest, the position of the interlobar pleura and location of the various lobes. On the left side the lung field is divided into an upper and lower lobe by a plane of pleura which extends forward and downward from the level of the 5th dorsal vertebra to the anterior margin of the diaphragmatic shadow. On the right side a middle lobe is formed at the expense of the upper lobe by an additional horizontal projection of a pleural plane progressing from the hilum region forward to the anterior chest-wall. With the X-ray tube centered at about the 5th dorsal vertebra, at 40 to 48-inch distance, as it usually is, the ray is projected along the plane of the interlobar pleura, and it is possible by a diagram to predict just what form consolidation of the various lobes will take. In upper-lobe consolidation the ray traverses consolidation of similar thickness throughout, so that the resulting

[1] From the X-ray Departments of St. Mary's Hospital and the St. Louis City Hospitals, St. Louis, Missouri.

[2] Read before the Mississippi Valley Conference on Tuberculosis, St. Louis, Missouri, September 26–30, 1927.

shadow on the X-ray film should be dense and homogeneous in appearance. The divergent beam of X-rays is projected across the lower border of the consolidation, so that the resulting shadow should have an abrupt straight-line border from the hilum to the periphery. In middle-lobe consolidation the consolidated area is smaller and is wedge-shaped. In this instance the ray traversing the consolidated area is most obstructed above, so that the shadow produced will be much denser above and will shade out below, extending from the hilum region to the periphery in the midportion of the chest, showing a straight-line upper border.

FIG. 1. SHADOWS CAST BY CONSOLIDATION OF DIFFERENT LOBES WITH USUAL CHEST TECHNIQUE CENTERING AT 5TH DORSAL VERTEBRA

A: Upper-lobe consolidation shows dense homogeneous consolidation of upper portion of chest with a straight-line lower border

B: Middle-lobe consolidation shows a small shadow extending from the hilum region to the periphery, densest above, having a straight-line upper border and feathering out into normal lung density below

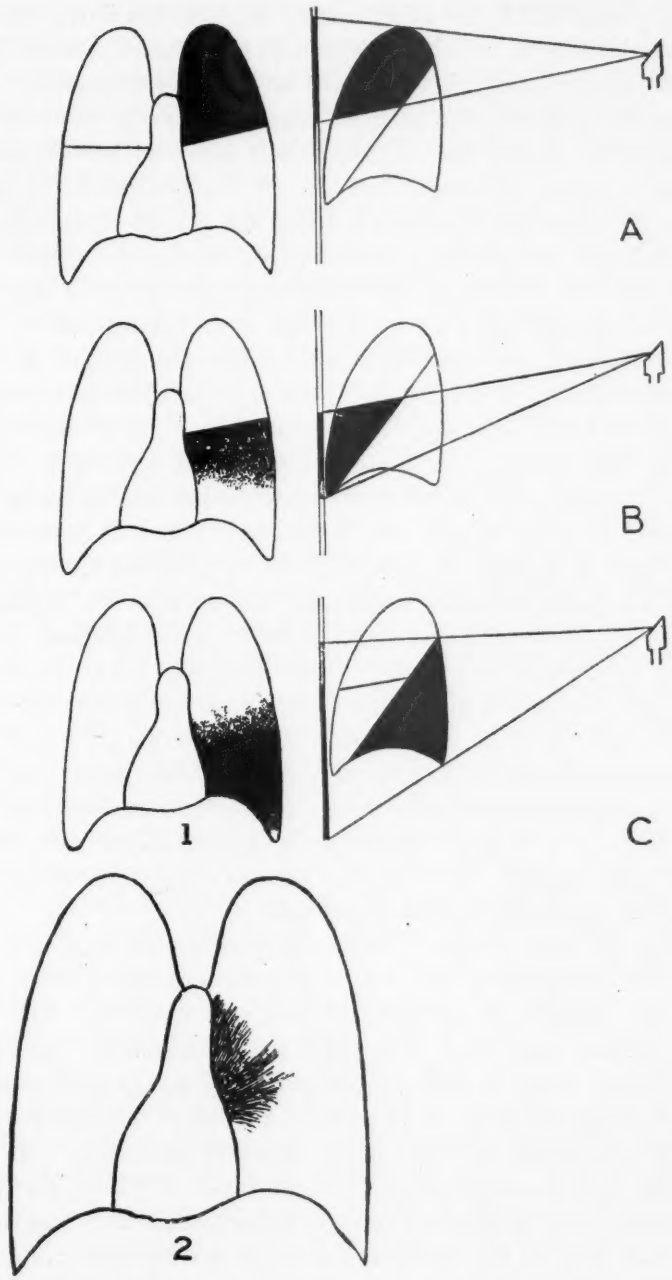
C: Lower-lobe consolidation shows a large shadow covering fully the lower two-thirds of the lung field, densest in its midportion and showing a hazy upper and hazy lower border where consolidation is complete. The costophrenic angle is last to become consolidated and often remains aerated throughout the course of the disease.

Acute caseous tuberculous pneumonia usually involves the right upper lobe, but may involve any of the lobes of the lung. It presents an appearance similar to that of lobar pneumonia.

FIG. 2. HILUM PNEUMONIA OR PNEUMONIA IN WHICH THE CONSOLIDATION IS CONFINED TO THE HILUM REGION

This may properly be considered as an abortive type of lobar pneumonia. Certain cases which we have encountered indicate that this form of pneumonia likewise may be of tuberculous origin. In children it may disappear, only to reappear several months later, ultimately resolving and leaving the patient in a healthy condition. In adults it may end in cavity-formation, dissemination of the disease and death.

The lower-lobe consolidations are much more extensive, and have wedge-shaped upper and lower borders, which result in an X-ray shadow which is very extensive, overlapping any possible middle-lobe involvement; densest in the midportion, and feathering out into normal lung density above and below. On the left side the upper lobe corresponds to the upper and middle lobes on the right, so that left upper-lobe consolidation would lack a straight-line lower border and would assume a hazy feathered-out appearance.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Lobar pneumonia in the adult usually starts in the hilum region, and spreads to involve an entire lobe within 24 to 48 hours. After full lobar consolidation, no change is noted until several days after crisis. During the state of resolution the resolving area acquires at times a mottled appearance not unlike that of tuberculosis and readily confusable with it. This is especially true if the site of the pneumonic involvement was the left upper lobe; on the right side the abrupt straight-line lower border will give an indication of the true nature of the disease, but on the left side this will be lacking. Reëxamination in 24 to 48 hours will show complete resolution if the condition is not tuberculosis.

It would hardly seem possible that lobar pneumonia could be confused with tuberculosis, and yet there is a form of tuberculous lobar pneumonia which is similar in all respects to pneumonia of pneumococcus origin. Clinically and even radiographically these forms may be indistinguishable. This form of acute caseous tuberculous pneumonia seems to occur in patients showing little, if any, evidence of previous tuberculous disease. There is usually no indication of tuberculosis elsewhere in the chest. Temperature, pulse, respiration, leucocyte count, clinical symptoms and physical signs, all are similar in the two conditions. Not until the time for crisis is long passed is the tuberculous nature of the disease suspected. True lobar pneumonia causes no actual destruction of tissue, so that resolution is prompt, leaving the lung structure intact; caseous tuberculous pneumonia, on the other hand, causes destruction of lung tissue, resolution always takes place with cavity formation, and healing is by fibrosis. Not until the stage of destruction do tubercle bacilli appear in the sputum. At this time evidence of extension of the infection also becomes apparent in the radiograph.

During the winter months, lobar pneumonia runs true to form, but during the remainder of the year many atypical forms make their appearance,—partial consolidation of various lobes, etc. In one form which we have seen most frequently, the consolidation remains in the hilum region, never spreading to the periphery and never showing lobar-pneumonic distribution. Such patients have all of the clinical symptoms of lobar pneumonia but none of the physical signs; they terminate by crisis and resolve completely in 10 to 14 days. We have always looked upon these cases as abortive types of lobar pneumonia; abortive in the sense that they do not go on to full lobar involvement but not in the sense of shortness of the disease. In children certain types of recurrent hilum consolidation have been encountered which have been definitely

proved as of tuberculous nature. In adults we likewise have reason to believe that at least some of these cases are of a similar nature to caseous tuberculous pneumonia. In a number of cases which we have encountered such hilum consolidation rapidly disintegrates, with cavity formation; tubercle bacilli appear in the sputum and there is a rapid dissemination of the disease and death.

Lung abscess of the pyogenic type may be acute or chronic. Radiographically, acute lung abscess starts as an area of definite consolidation in the lung, frequently in the hilum region, and soon develops an area of rarefication in its midst. The consolidation spreads slowly, and rarely if ever takes on true lobar characteristics. During the acute stage there is a heavy wall of infiltration thrown about the abscess cavity which usually serves to distinguish it from tuberculosis. When a lung abscess becomes chronic, however, the problem may be more difficult; radiographically the cavity wall becomes thinned out, and if the abscess is in the upper lobe there may be some difficulty in deciding its true nature. Usually, however, tuberculosis which has progressed to the stage of cavity formation has other associated evidences of the disease. Clinically the symptoms of lung abscess may be so much like those of tuberculosis that differentiation is almost impossible. Radiographically the resemblance may be so great that the finding of tubercle bacilli in the sputum may be the only means of differentiation. If repeated examination fails to reveal tubercle bacilli, this is an argument highly in favor of the pyogenic nature of the disease.

Abscess of the lung may be of primary origin, or may result from pneumonia or other inflammatory lesions in the chest. Such abscesses may be small and multiple, involving a large quantity of lung tissue, even an entire lung. Nature, in an effort to wall off the infectious process from the surrounding lung, throws out a barrier of fibrous tissue around each abscess. The pus thus becomes permanently entrapped, the fibrous tissue becomes organized and is replaced by scar-tissue. Scar-tissue, wherever it occurs, contracts; as a result of its contraction in this location there is a narrowing of the involved side of the chest and approximation of the interspaces; the heart and mediastinal structures are pulled over toward the involved side and there is elevation of the diaphragm. The contractile action of the scar-tissue is likewise manifested in the formation of numerous bronchiectatic cavities from traction on the bronchial walls. This condition produces a characteristic radiographic picture,—a dense shadow involving all or the major portion of

one lung, mottled by numerous bronchiectatic cavities showing throughout its entire extent narrowing of the involved side of the chest, approximation of the interspaces, displacement of the heart and mediastinal structures toward the involved side, and elevation of the diaphragm. This is the picture of chronic interstitial pneumonia. It may be entirely of pyogenic origin, or it may be the result of extensive tuberculous in-

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FIG. 3. *A:* LUNG ABSCESS OF THE ACUTE TYPE

This presents a wide zone of infiltrations surrounding the abscess cavity and will rarely be confused with tuberculosis

B: LUNG ABSCESS OF THE CHRONIC TYPE

This lacks the zone of inflammation found in acute abscess and may be very difficult to differentiate from tuberculous cavity

FIG. 4. CHRONIC DIFFUSE FIBROSIS (CHRONIC INTERSTITIAL PNEUMONIA), SHOWING PICTURE SIMILAR TO MASSIVE COLLAPSE EXCEPT THAT IN THIS INSTANCE THERE IS ASSOCIATED CAVITY-FORMATION

There are narrowing of the involved side of the chest, retraction of the heart and mediastinal structures toward the involved side and elevation of the diaphragm

FIG. 5. MASSIVE COLLAPSE OF THE LUNG, SHOWING DENSE HOMOGENEOUS SHADOW, WITH NARROWING OF THE INTERSPACES, ELEVATION OF DIAPHRAGM AND RETRACTION OF TRACHEA

There is no evidence of cavity-formation

FIG. 6. *A:* LOBAR PNEUMONIA, SHOWING STRAIGHT-LINE LOWER BORDER AND HOMOGENEOUS SHADOW; NOT DISTINGUISHABLE FROM TUBERCULOUS CASEOUS PNEUMONIA

Clinical course differentiates conditions

B: PRIMARY TUMOR OF LUNG, THE HOMOGENEOUS SHADOW HAVING NO DEFINITE LINE OF DEMARCATION FOR LOWER BORDER AND FEATHERING OUT INTO NORMAL LUNG DENSITY BELOW

No displacement of mediastinal structures

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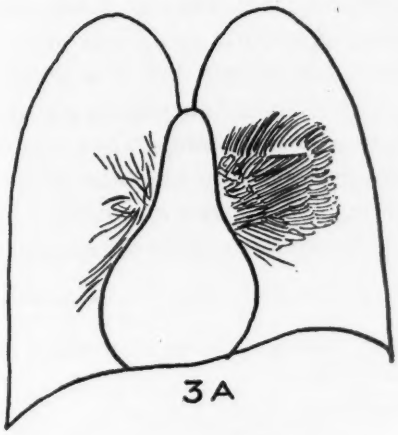
fection. The radiographic picture may be almost the same in both instances. When the condition is the result of tuberculosis, however, there is usually evidence of extension of the disease to the opposite lung; when the condition is not the result of tuberculosis the opposite lung remains free from disease even for years.

The next condition to which I wish to call attention is *massive atelectatic collapse* of the lung. This is an acute condition in which, without



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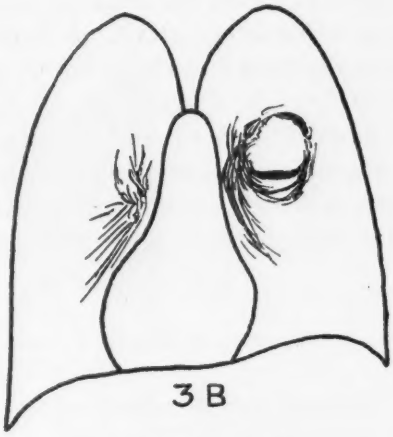

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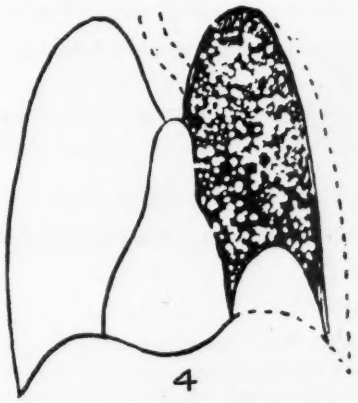

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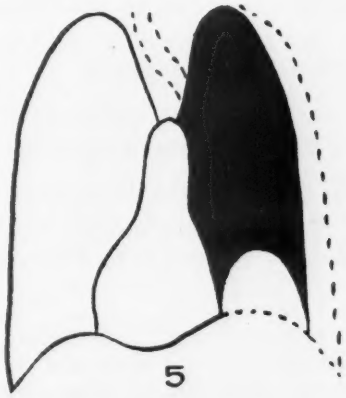

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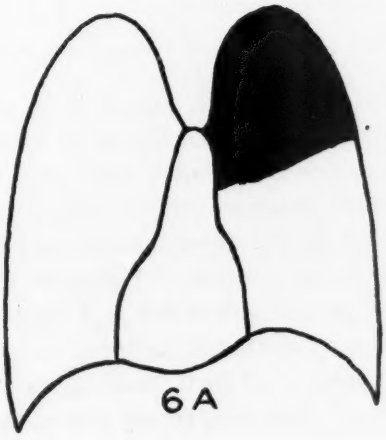

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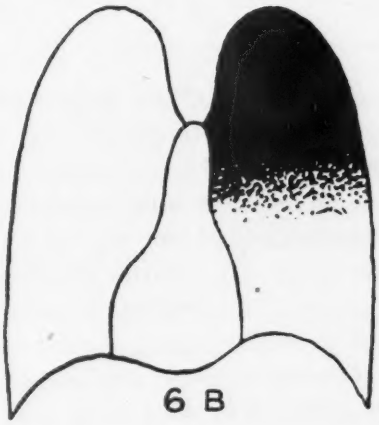

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apparent cause, the lung, previously well aerated, loses its air-content and becomes atelectatic. It is not very likely that this might be confused with any of the ordinary types of tuberculosis, but it is possible that it might be mistaken for the acute caseous tuberculous variety. The condition is encountered most frequently as a postoperative complication after abdominal operation. Radiographically an entire lobe or lung is densely solidified and homogeneous in appearance, and there are narrowing of the involved side of the chest, approximation of interspaces

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FIG. 7. FLUID FREE IN GENERAL PLEURAL CAVITY, OBSCURING COSTOPHRENIC ANGLE, AND WITH CURVED UPPER BORDER

Displacement of the mediastinum not always present

FIG. 8. *A:* LOCALIZED PLEURAL EFFUSION UNASSOCIATED WITH PLASTIC FIBRINOUS PLEURISY

Note smooth border and rounded outline, with base at the periphery and inward bulge toward the compressible lung

B: LOCALIZED PLEURAL EFFUSION ASSOCIATED WITH PLASTIC FIBRINOUS PLEURISY

Note ragged outline of the shadow

FIG. 9. GENERALIZED INFILTRATIONS UNIFORMLY DISTRIBUTED THROUGHOUT BOTH LUNGS

These may be due to miliary tuberculosis, disseminated pulmonary tuberculosis, miliary carcinomatosis, second stage of silicosis, or bronchiolitis

FIG. 10. PNEUMOTHORAX

A frequent complication of pulmonary tuberculosis. With the collapse of the lung it is removed from the chest-wall and physical examination can no longer detect the condition of the lung; radiographic examination can to some extent reveal conditions present in the lung, and may disclose the cavity which gave rise to the pneumothorax.

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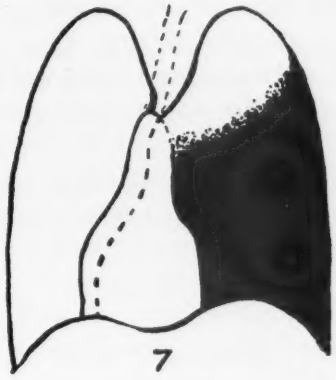
and elevation of the diaphragm. The radiographic picture is in all respects similar to chronic interstitial pneumonia, except that no bronchiectatic cavities are present; likewise, this condition is acute and is not preceded by other pulmonary disease, whereas chronic interstitial pneumonia is of long standing and follows other pyogenic infection of the lungs. As a matter of differentiation and a means of treatment we have found that rolling the patient upon his uninvolved side and causing him to cough results in almost immediate reinflation of the lung.

Primary tumors of the lung may, on account of their insidious onset, be suspected as being tuberculous disease. This is especially true of the



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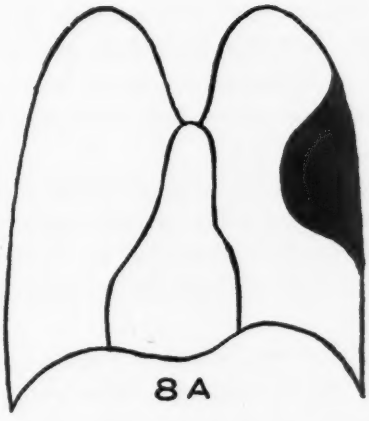

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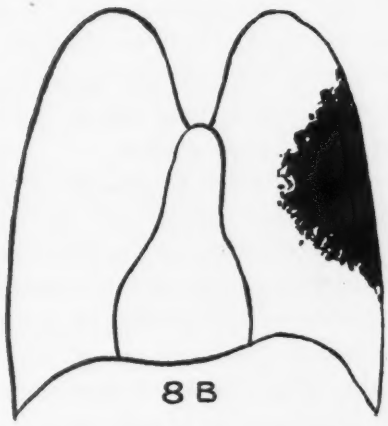

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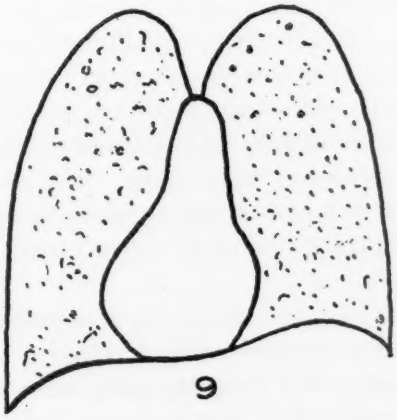

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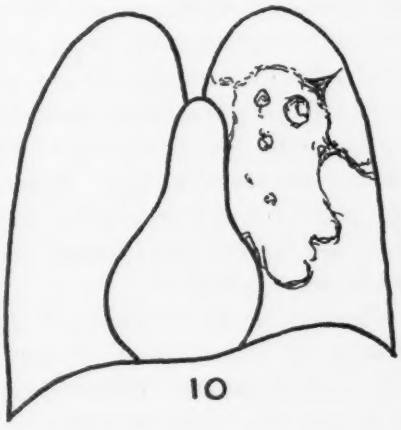

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diffuse type of primary carcinoma of the lung, which progresses slowly, gradually invading larger areas of lung tissue; such tumors sweep on across intervening pleural septa and present an infiltrating hazy border. While they may after months show some tendency to disintegrate and form cavities, the cavities thus formed are always small in comparison with the extent of pulmonic consolidation and are always more ragged and irregular than those encountered in tuberculous caseous pneumonia.

None of these diseases, with the exception of lobar pneumonia of the upper lobes in its resolving stage, would ever be confused with the ordinary infiltrative types of tuberculosis. In a large majority of instances infiltrative tuberculosis starts in the upper lobes, a condition which fortunately does not prevail in any other disease which resembles tuberculosis. Bronchopneumonia forms similar infiltrations, but these usually predominate in the lower lobes. Primary lower-lobe tuberculosis may take on the appearance of bronchopneumonia or even of secondary malignant tumor, but this form of tuberculosis is so rare as to be entirely negligible.

The uniform dissemination of *small infiltrations* throughout both lungs, such as that encountered in the disseminated form of pulmonary or miliary tuberculosis, may be encountered in the second stage of silicosis, miliary carcinomatosis, or bronchiolitis. The clinical history may be decisive in differentiating these conditions.

Pleural effusion is one of the conditions upon which a diagnosis of pulmonary tuberculosis may be based. Pleural effusions, either general or local, may be of nontuberculous origin. Tuberculous effusions bear no distinctive characteristics; they usually consist of thin serous fluid, however, and rarely tend to pocketing. Any tendency of fluid to become localized is presumptive evidence of its nontuberculous nature. Fluid free in the pleural cavity, regardless of its cause, takes on a hazy concave upper border, extending from the hilum upward and outward to the axilla. Localized pleural effusions, wherever they occur, have one characteristic: they produce a shadow with base at the periphery of the lung, and bulge inward toward the compressible lung with a rounded semicircular border.

Spontaneous pneumothorax is also a frequent complication of tuberculosis but it is likewise frequently encountered without reference to tuberculous disease. With the collapse of the lung, the latter retracts from the chest-wall, and physical examination can no longer detect

pathological changes in the lung. Radiographic examination shows something of the condition of the collapsed lung, and often locates the cavity which gave rise to the pneumothorax.

Pulmonary tuberculosis manifests itself in such numerous ways that, even with every method at our command, the problem of diagnosis is at times very difficult. The free use of X-ray examination proves a valuable aid in the diagnosis of this multiform disease.

THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF PLEURISY IN PULMONARY TUBERCULOSIS[1]

FRED H. HEISE AND LAWRASON BROWN

In the ordinary course of pulmonary tuberculosis pleurisy is of rather frequent occurrence, so much so that one would imagine that its presence might be of some value in the diagnosis of this disease and perhaps also influence its course. Several methods of determining the occurrence, past or present, of pleurisy are at our disposal. Thus we may have from the patient a history of chest pain increased upon inspiration, especially when forced, or there may be evidence of physical signs, such as impaired note and distant breathing or perhaps a definite friction rub, movable dulness, etc. The X-ray may reveal definite uniform clouding or there may be adhesions demonstrated both on the plate and in the fluoroscope. Exactly how much value any of the above findings may be in the diagnosis or prognosis of pulmonary tuberculosis is most difficult to determine. Nevertheless, a study of the frequency of occurrence of various phenomena of pleurisy and their correlation may be of some assistance.

All pain in the chest occurring in the tuberculous is, of course, not attributable to involved pleura. Nor are all pleurisies necessarily accompanied by pain. A pulmonary lesion may cause painful and tender sensations in the skin overlying or adjacent to it by a reflex action in the spinal nerve roots, although the lung tissue has no distinct pain sense (the referred pains of Head). When the lung has been collapsed by the administration of air, the visceral pleura may be irritated without any sense of pain on the part of the patient, whereas irritation of the parietal pleura or diaphragm is immediately accompanied by pain, which may be referred to a location far removed from the seat of irritation and depending upon the part of the diaphragm irritated, or which may be distinctly localized at the site of irritation of the parietal pleura (Capps). Thus pleurisy may be present with or without chest pain or with pain at a location other than in the chest, as, for instance, in the neck or abdomen. The interpretation of pain in terms of pleurisy therefore must remain on

[1] From the Trudeau Sanatorium, Trudeau, New York.

an inexact basis. In addition, other conditions affecting the nervous system, especially the intercostal nerves, are often the cause of pain in the region of the chest. So, too, myositis may cause chest pain which may be aggravated by all muscular action, including breathing. Nevertheless, pain which is aggravated by breathing, and which is localized, should be regarded as due to pleurisy until proved otherwise. Pleurisies may entirely disappear or resolve. This can be demonstrated by the fact that an unsuccessful attempt at artificial pneumothorax may at a later date prove successful. Whether friction is necessary to produce pleural pain is doubted by Bray, who thinks that inflammation with stretching of the parietal pleura during inspiration suffices.

Distant breathing and impairment of note do not always indicate pleurisy and may be present when marked infiltration of the lung alone is presumably present. The physical signs may disappear as the infiltration recedes, but it can be said that any infiltration lying so near the surface as to produce dulness in all probability involves the pleura. Localized dulness and distant breathing in the lower portion of the chest, without similar phenomena in the upper, however, usually mean pleurisy or an effusion in the cavity.

The existence of a pleurisy cannot always be determined by the X-ray. Evidence of this is seen when artificial pneumothorax cannot be established although no X-ray evidence of pleurisy can be seen. Nevertheless a homogeneous clouding is strongly suggestive and the characteristic curve, when fluid occurs, with its crown in the axilla where the lung collapse is greatest, will appear when the quantity is sufficient. Past or present pleurisies may be indicated by adhesions seen by fluoroscope and on the plate, and by thickening of the interlobar fissures and pleural caps. Pleural caps were thought by Van Zwaluwenburg, who first described them, to prove that tuberculosis of the lungs arose at the caps from infection of the cervical lymph nodes.

How often can pleurisy be demonstrated by any or all of these methods in pulmonary tuberculosis?

Pulmonary tuberculosis could not be satisfactorily demonstrated in 319 patients entering Trudeau Sanatorium. Of these, 181 (57 per cent) gave a history of having had pain in the chest and 4 (1 per cent) had a demonstrable effusion. From this one would naturally conclude that pain in the chest was of no great practical significance in determining the presence of pulmonary tuberculosis. Of the above, 11 (5 per cent) nontuber-

culous patients stated that the onset of their invalidism was with pain in the chest.

No definite evidence of tuberculosis could be found in 162 cases, but the patients were classified as "suspects" because they had had haemoptysis or pleurisy with effusion or a history of tubercle bacilli being found once; or for some other reason. Pain in the chest occurred in 104 (64 per cent), or slightly more frequently than in the nontuberculous. Effusion occurred in 25 (15 per cent). This frequency is high because when no cause for the pleurisy could be found the patient was classified as a suspect.

The proved cases of tuberculosis numbered 1,849 and included 276 minimal, 1,358 moderately advanced and 215 far advanced cases, all of which were classified according to the American Sanatorium Association standards of 1922, including X-ray examination. Pain in the chest occurred as follows: Minimal, 168 (61 per cent); moderately advanced, 950 (70 per cent); and far advanced, 148 (69 per cent): a fairly uniform occurrence despite the extent of the disease and not very much greater in frequency (13 per cent) than that of the nontuberculous group. The same uniform frequency was found in the occurrence of pleurisy with effusion, the figures being minimal, 12 (4 per cent); moderately advanced, 70 (6 per cent); and far advanced, 10 (5 per cent). However, when we consider the total number of pleurisies with effusion, 121, we find that 3 per cent occurred in the nontuberculous, 21 per cent in the "suspects," 10 per cent in the minimal, 58 per cent in the moderately advanced and 8 per cent in the far advanced. It is interesting to note that the moderately advanced cases represented 58 per cent of the total number of all cases. About three-fourths of the pleurisies with effusion occurred when definite pulmonary tuberculosis was present. This latter group comprised 79 per cent of all the cases. So it appears that the occurrence of a pleurisy with effusion is of value in making a diagnosis of pulmonary tuberculosis in the patient entering a sanatorium. Onset of the disease with chest pain or pleuritic effusion was said by the patient to have occurred in 8 per cent of the "suspects," 10 per cent of the minimal, 7 per cent of the moderately advanced and 8 per cent of the far advanced, a rather uniform rate.

It was proved by the experimental work of Paterson that pleurisy with effusion, due to tuberculosis, is produced experimentally only in the presence of hypersensitiveness. This sensitiveness, however, need not be produced by living microörganisms, as has been shown recently by

Petroff. This experimental work, however, does not prove that an individual must have been tuberculous to have developed tuberculous pleurisy with effusion.

In a series of patients who entered the sanatorium previous to the use of the X-ray, 241 mentioned the location of the pleuritic pains. This was unilateral in 193 (80 per cent) and bilateral in 48 (20 per cent). Of the unilateral cases, distant breathing occurred on the same side in 61 (32 per cent) and on the opposite side in 25 (13 per cent). A friction rub was heard on the same side in 6 (3 per cent) and on the opposite side in 1 (0.5 per cent). Distant breathing and a friction rub were absent in 51.5 per cent. This is in part explained by the interval of time between the onset of pain and the patient's entrance into the sanatorium. Of 48 cases in which bilateral pain occurred, only 21 per cent had bilateral distant breathing, 48 per cent had unilateral distant breathing and 2 per cent unilateral friction rub. When the location of the pain was not mentioned, as occurred in 129 instances, 42 per cent had distant breathing or a friction rub.

In another series of 106 cases, all of which were examined by X-ray, 87 had a history of chest pain and 57 (66 per cent) of these showed adhesions or other evidence of pleurisy; and 59 (68 per cent) had distant breathing, though not always on the same side nor similarly unilateral and bilateral. Variation in the location of pain, distant breathing and the X-ray evidence reached as high as 40 per cent.

Distant breathing occurred in 75 instances and 52 (61 per cent) had also X-ray evidence of pleurisy. X-ray evidence of pleurisy was seen in 71 instances, of which 80 per cent had pain and 73 per cent distant breathing; so that, for the most part, chest pains were indicative of pleurisy which could be determined by other means. Although a history of pain was obtained from the patient, or distant breathing was found upon examination, 35 of the 106 (33 per cent) cases showed no X-ray evidence of pleurisy. Pain alone had been present in 12 (34 per cent) of these, distant breathing was present alone in 5 (14 per cent), and both were present in 18 (51 per cent).

Where almost every alternate patient has had what may be interpreted as dry pleurisy or pleuritic pain, it is almost impossible to determine its prognostic significance. However, for the period 1905–1915 death from tuberculosis occurred within five years in 7 per cent of the incipient, 24 per cent of the moderately advanced and 62 per cent of the far advanced. In those having had pleuritic pain the figures were 8 per

cent of the incipient, 26 per cent of the moderately advanced and 33 per cent of the far advanced. The far advanced cases apparently did not fare worse by reason of their pleurisy pains.

For the years 1916–1919, when X-rays were used in all instances, and when all cases were classified according to the American Sanatorium Association standards of 1922, mortality from tuberculosis occurred within five years as follows: Minimal, 5 per cent of 285; moderately advanced, 13 per cent of 1,073; far advanced, 31 per cent of 206 cases. In those having pleurisy with effusion the mortality was for the minimal, none; for the moderately advanced, 8 (27 per cent); and for the far advanced, 2 (100 per cent). The number of cases in this series, however, is regrettably small, there being only 9 minimal, 29 moderately advanced and 2 far advanced. Nevertheless, the mortality in the moderately advanced group suggests that those with pleuritic effusion do not fare well in the outcome of their tuberculosis. When those who have had pleuritic effusion without other demonstrable evidence of pulmonary tuberculosis are considered, we find that death from tuberculosis within five years took place in only 1 of 15 instances, or 7 per cent, behaving very much like the minimal group.

Of 20 patients who had pleurisy with effusion at some time, X-rays on discharge, taken about six months after entrance X-rays, showed that the lung lesion remained stationary in 5 (25 per cent). An actual lessening of inflammation took place in 12 (60 per cent), whereas 3 (15 per cent) showed an increase of tuberculosis. It would seem that temporarily at least these patients do not behave very differently from the average.

Only 4 of the 75 patients had cavities in the lungs discoverable by X-ray, the nodular productive type predominating as it does with all cases entering Trudeau. Râles, tubercle bacilli, haemoptysis occurred with the same frequency in the exudative pleurisy cases as was found in all tuberculosis cases entering Trudeau during the same period, 1916–1919, inclusive, with two exceptions. The minimal cases with pleurisy with effusion had a lower percentage of râles than for all minimal cases (33 per cent versus 57 per cent), and the moderately advanced cases with pleurisy with effusion had a lower positive-sputum record than was found in all moderately advanced cases (60 per cent versus 70 per cent).

One would naturally think the minimal and moderately advanced cases, having had pleurisy with effusion, would show a lower mortality

and relapse rate than the average. This does not hold true, however, in later years.

Just what pleurisy with effusion means in the course of pulmonary tuberculosis has not been fully determined. Is it an expression of heightened local resistance to a new infection? Certainly it should be more prevalent were it the expression of heightened resistance, inasmuch as the pleurae are so frequently involved in all cases of pulmonary tuberculosis including those that do especially well. Does dosage of tubercle bacilli play the important rôle? After the effusion has formed is the beneficial effect of lung collapse counterbalanced by subsequent adhesions preventing contraction of the lung by fibrosis in the diseased areas or hindering lymphatic drainage? All of these questions have not as yet been satisfactorily answered.

TUBERCULOSIS COMPLEMENT-FIXATION REACTION

In the minimal group of 12 cases only 6 had definite parenchymatous X-ray lesions, so that some doubt could be thrown upon the diagnosis in the remaining six. However, 67 per cent of these minimal cases, and 74 per cent of 19 "suspected" cases, had a negative complement-fixation reaction upon entrance to Trudeau. The reverse took place in the moderately advanced. In these 37 cases, 70 per cent had a positive reaction. Apparently the pleurisy with effusion *per se* does not inhibit complement-fixation reactions. There seemed to be almost an equal frequency of positive and negative reactions for the entire 75 cases.

Altogether it would seem that the occurrence of pleurisy with effusion exerts but little influence on the prognosis of any individual case of pulmonary tuberculosis for the first five years after discharge.

THE PROGRESSION OF LESIONS IN ACTIVE PULMONARY TUBERCULOSIS

FRED H. HEISE[1]

It is recognized that pulmonary tuberculosis may advance in several ways, some being much more rapid than others. Thus, extension of the disease may be brought about by means of the blood-vessels or by the air-passages or by the lymphatic system. When brought about by the vascular system there may be unilateral or bilateral pulmonary miliary tuberculosis, usually involving the whole of one or both lungs, or occasionally merely a localized condition. When extension takes place by means of the bronchi, both lungs may be extensively involved, as sometimes follows upon haemoptysis, or more generally there is a localized involvement affecting usually the lower half or two-thirds of the lung in the form of a bronchopneumonia. Following upon haemoptysis an extension may involve hitherto unaffected areas of lung with equal if not greater frequency than the previously diseased areas. Bronchogenic spread from aspirated sputum may produce localized areas or new foci within or remote from the area of previous disease. In the vascular or bronchogenic methods of extension, new foci may be established at a distance from established disease, since the bronchi afford many avenues and the blood-vessels act as carriers to all portions of the lungs.

When extension takes place by means of lymphatics, the disease should extend toward the root of the lung, as the drainage is in this direction. However, this apparently takes place only rarely. Extension of the disease locally, with obstruction of the smaller lymphatics, may occur retrogressively or toward the periphery. This apparently happens more frequently. There is however an extension of the disease by direct contiguity. This is probably lymphatic or bronchogenic in nature, and is likewise apparently the most frequent manner of advance in the chronic adult forms of tuberculosis.

An attempt was made to determine the frequency of extension of disease locally and in new areas by carefully examining the X-ray films

[1] Trudeau Sanatorium, Trudeau, New York.

showing definite progressive changes within the lungs and pleura of 152 patients. Of these only 32 had unilateral disease at the first examination and the remaining 120 had bilateral disease.

It was found that progression of the disease was manifested only by the development or increase of pleuritic densities in 27 instances, or about 18 per cent. Increase in the size of cavities without further infiltration was noticed in 12 instances, or 8 per cent. The remaining 113, or 74 per cent, were found to have a definite increase in collateral infiltration, or a development of new mottling or discrete tubercles.

Of these 113 cases there were 21 with unilateral and 92 with bilateral disease. It was interesting to find that of the unilateral cases the extension occurred within or immediately contiguous to the existing disease in 14 instances, or 67 per cent. Only 33 per cent developed new areas situated remotely from the old disease. Five of the seven new areas were on the opposite side.

Of the 92 bilateral cases extension occurred immediately contiguous to or within the area of existing disease in 65, or 71 per cent. New areas, remote from the old disease, were found in the remaining 27, or 29 per cent.

It would seem, therefore, that the most frequent manner of extension in the chronic adult type of pulmonary tuberculosis is by direct contiguity, that is, by what may be most easily interpreted as lymphatic extension.

There seemed to be no definite type of changes about the site of the old disease. In some instances there seemed to be a definite improvement in one portion while the other showed extension of disease. In other instances the old lesion seemed to remain unchanged except for the advance; in others the entire area showed intensification of shadows. Of 64 instances of bilateral disease in which definite increase in infiltration or collateral inflammation was seen, progression of the disease was found on both sides in 16 (25 per cent). The opposite lung showed no change in 25 (39 per cent). There was an improvement on the opposite side in 19 (30 per cent). In 3 (5 per cent) improvement was seen on both sides, and in one the opposite side remained unchanged while the same area showed extension and retrogression in different parts. Thus it can be seen that pulmonary tuberculosis may progress and retrogress in different areas or the same area at approximately the same time. Two pathologically active lesions may therefore behave in an opposite manner.

SOME CHEMICAL CHANGES ACCOMPANYING THE GROWTH OF TUBERCLE BACILLI ON LONG'S SYNTHETIC MEDIUM[1,2]

A Preliminary Study

TREAT B. JOHNSON AND ALICE G. RENFREW[3]

The organized program of research, which has been carefully laid out for the intensive chemical and biological study of tubercle bacilli,[4] has called for the production of large quantities of these bacteria. All of the bacilli produced for our investigation have been grown on a special synthetic medium[5] and have been supplied to us by the H. K. Mulford Company of Glenolden, Pennsylvania.[6]

The splendid facilities provided to-day by commercial organizations for the production of bacteria in sufficient quantities for extensive chemical research have not only given a new impetus to the chemical studies dealing with the composition of bacterial cells, but have also furnished us an unusual opportunity for carrying out a systematic chemical study of the more important metabolic changes characterizing especially the growth period of the tubercle bacilli. While this latter phase of bacterial analysis is somewhat outside the scope of our original program of tuberculosis research, we have considered it of sufficient importance, however, to institute a preliminary investigation of growth conditions, and have obtained as a result new data which promise to be of immediate value. It is not improbable that the end of the life-period of maximum growth in any bacterial culture may be revealed by chemical tests, and the preliminary data indicate that a practical method of assaying culture growths is possible of accomplishment.

The puzzling phenomena associated with the growth of bacteria cannot

[1] From the Department of Chemistry, Yale University.

[2] Aided by a grant from the National Tuberculosis Association.

[3] National Tuberculosis Association Research Fellow, 1927–1928.

[4] An investigation of a coöperative nature which is supported by special grants from the National Tuberculosis Association.

[5] Long's synthetic medium, as described in *Tubercle, 1924, vi, 128.*

[6] We desire to express our appreciation of the coöperation and support of this commercial organization in this research.

be accurately accounted for chemically so long as the media employed in growth are so complex in composition. The introduction of the newer methods of technique, whereby synthetic media of known composition are utilized for growth in place of media of unknown composition, has opened up an avenue of research for the chemist which promises to lead to results of fundamental importance. Even under these improved conditions we are still confronted with many difficulties to be overcome before we can present a picture of the fundamental chemical changes taking place in growth. Long (1), who has studied extensively the nutritional factors governing the growth of tubercle bacilli writes as follows: "I confess that so far I have only accumulated many details without being able to establish broad, general principles with which details may be correlated."

Previous investigators of tubercle bacilli have been interested chiefly in the nature of the substances which are essential in the growth of this microörganism and the rôle of glycerol which, as is well known, favors luxuriant growth. Furthermore, each investigation reported has considered only a restricted number of factors, and has generally been limited in scope by time, bacterial material available for research, difficulties of manipulation, and by the special interests of the respective worker. One of the most extensive researches in this field has been carried out by Long and his associates (2) in an attempt to determine, if possible, in what manner essential constituents of synthetic media are used in bacillary growth.

In investigations dealing with reaction changes in the culture medium during the growth of tubercle bacilli, the chemical problem has been extremely puzzling, and the various studies in this field have generally dealt with some phase of the phenomena which we express graphically by the Theobald Smith curve. Notwithstanding all the work that has been contributed on this subject we are still unable to give to-day a satisfactory chemical explanation of these phenomena. The study of this problem has been necessarily a difficult one, on account of the fact that most of the work has been done with media containing proteins or peptones in the nutrient or culture broth. In fact, so far as the writers are aware, no exhaustive study has ever been made of the growth of any specific bacterium on synthetic media free from proteins and carbohydrates. The object of the research discussed in this paper was to obtain, if possible, significant data which would serve to elucidate the chemistry of some of these growth changes.

EXPERIMENTAL PART

Medium Used and Conditions of Growth: The cultures of tubercle bacilli employed in this research were inoculated and grown in the laboratories of the H. K. Mulford Company at Glenolden, Pennsylvania. The medium used was that recommended by E. R. Long (3). Two hundred cubic centimetres of this synthetic medium were placed in each culture bottle, inoculated with tubercle bacilli (human strain H37), and incubated under sterile conditions at 37°C. Two bottles of this medium were reserved for analysis to serve as controls. Each successive week for a period of two months after the initial inoculation, duplicate samples of the growing cultures were removed from the incubator, shaken to submerge the bacilli, tightly corked and preserved in cold storage for future chemical work. Four culture bottles were left undisturbed; two of these were removed after three months and two were incubated for a total period of four months. Approximately four to six weeks elapsed between the time the respective culture bottles were sealed and placed in cold storage and the time these same bottles were opened for final analysis.

Technique Used in the Preparation of Cultures for Analytical Determinations: Immediately after opening each bottle 2 cc. of the clear medium was used for a colorimetric determination of pH. The bacteria were then collected by filtration of the medium through fused, porous glass plates, washed with distilled water, and finally dried in an Abderhalden vacuum drier at 60° in the presence of "dehydrite." The filtrate and washings were then transferred to a 250-cc. volumetric flask and diluted to volume; a surface layer of toluene was finally added to preserve sterility. The flasks were then uniformly plugged with cotton, and heated for one hour at 60° and preserved in sterile condition for analytical work.

As bottles representing longer periods of incubation were examined, it was soon found that, with cultures in which considerable growth had occurred, the above method of filtration became entirely impracticable, and we were compelled to use a centrifuge for separation of the bacilli. The microörganisms were then transferred to porous glass filters or hardened filter papers for thorough washing. This was continued in all cases until the washings failed to give an appreciable test for ammonia with Nessler's reagent.

Methods Used in Quantitative Determinations: 1: The weight of bacilli

filtered from each bottle was determined after drying in a vacuum to constant weight at 60°.

2: The pH was determined colorimetrically on 2-cc. aliquots of the medium immediately after opening each culture bottle, and again on 2-cc. aliquots after filtration and sterilization. In most cases the pH was unchanged after heating, but, as the quantity of protein in the medium increased, the direct determination of the pH on the culture itself was difficult to read accurately. This difficulty, however, was not encountered after the medium had been heated to 60°. The buffer solutions for the colorimetric standards were made up according to Clark and Lubbs's directions (4). The indicators used were brom-phenol-blue, brom-cresol-green and chlor-phenol-red.

3: Ammonia was determined in duplicate 25-cc. aliquots of the medium by distillation in the usual manner in the presence of magnesium oxide. When frothing was troublesome during the distillation, it was easily remedied by the addition of 15–20 cc. of pure alcohol. Distillation with MgO does not liberate an appreciable amount of the amide nitrogen of the asparagin used in the medium. For example, in the distillation of 0.4530 gm. of pure asparagin dissolved in 25 cc. of water, with magnesium oxide only 0.0003 gm. of ammonia was detected by titration, whereas the theoretical amount available from this source is 0.0583 gm. The only sources of free ammonia by distillation of the Long medium with magnesium oxide are the ammonium salts of iron and ammonium citrates.

4: The inorganic phosphate plus a small amount of phosphorus from suspended or colloidal organic material was weighed as magnesium pyrophosphate after an initial precipitation as ammonium phosphomolybdate. The technique applied to a 25-cc. aliquot involved the destruction of organic matter by oxidation with concentrated nitric acid in the presence of 2–3 drops of sulphuric acid and finally digestion for several hours on an electric stove. Duplicate determinations were made on both culture flasks for each week of the early growths. For later weeks single determinations were made on each bottle unless an apparent discrepency was noted in the analytical data for the two bottles for any given week.

5: Reducing substances present in the filtrates after treatment with tungstic acid were determined by the Shaffer-Hartmann (5) microchemical method. The proteins were removed from solution according to the

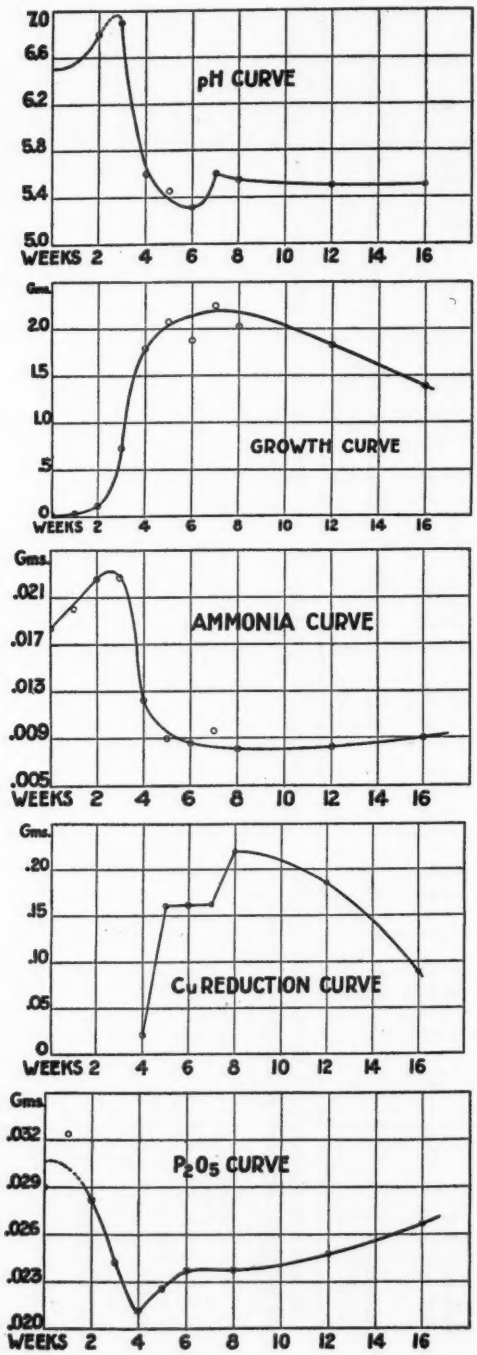
TABLE 1

Quantitative data obtained during growth of tubercle bacilli (strain H37) on synthetic medium

SAMPLES IN DUPLICATE	TIME OF GROWTH	pH AFTER END OF GROWTH-PERIOD	pH AFTER DILUTION TO 250 CC. AND HEATING AT 60°	SUGAR BY SHAFFER-HARTMANN METHOD		NH_3 IN 25 CC. ALIQUOT DISTILLATION OVER MgO	P_2O_5 IN 25 CC. ALIQUOT	WEIGHT OF BACILLI DRIED AT 60°	COAGULATION OF PROTEIN AFTER HEATING	FOLIN PHOSPHO-TUNGSTIC ACID COLOR REACTION
				Cu per culture bottle	Reducing sugar					
	weeks			*grams*	*grams*	*grams*	*grams*			
200 cc. volume per culture unit.		6.5	6.5			0.0197	0.0289			
Blanks 1–2		6.5	6.5			0.0167	0.0290			
Culture A 1	1	6.6	6.6			0.0211	0.0326?	0.050		
2		6.5	6.5			0.0206	0.0322?	0.026		
Culture B 1	2	6.8	6.8			0.0212	0.0290	0.122		
2		6.8	6.8			0.0240	0.0277	0.100		
Culture C 1	3	6.9	7.0			0.0225	0.0262	0.719	Very slight	+ (?)
2		6.9	6.9			0.0228	0.0225	0.766		
Culture D 1	4	Lost	6.0	0.022	0.014	0.0129	0.0211	1.619	Slight	+
2		5.6	5.6			0.0115	0.0213	1.990		
Culture E 1	5	5.4	5.4	0.185	0.081	0.0083	0.0222	2.12	Heavy flocculation	++
2		5.5	5.5	0.140	0.062	0.0097	0.0232	2.03		
Culture F 1	6	5.3	5.3	0.172	0.076	0.0084	0.0238	1.93	Heavy flocculation	+++
2		5.3	5.4	0.152	0.068	0.0087	0.0236	1.82		

Culture G	1	7	5.6	5.8	0.163	0.072	0.0099	Lost	2.09	Medium flocculation	++++
	2		5.6	5.8	0.088?	0.041?	0.0093	0.0247	2.41?		
Culture H	1	8	5.6	5.7	0.205	0.090	0.0081	0.0237	1.55?	Medium flocculation	+++++
	2		5.5	5.4	0.237	0.102	0.0081	0.0239	2.03		
Culture I	1	12	5.5	5.5	0.225	0.097	0.0090	0.0237	1.67	Medium flocculation	++++
	2		5.5	5.5	0.147	0.066	0.0079	0.0241	2.00		
Culture J	1	16	5.4	5.3	0.067	0.033	0.0097	0.0258	1.23	Slight flocculation, liquid cloudy	+++
	2		5.6	5.4	0.142	0.063	0.0084	0.0274	1.53		

Comments: Culture C: Encountered first difficulty in filtering. Only a trace of coagulated protein was obtained. Culture D: Increase in quantity of coagulable protein quite apparent.


7.0
6.6
6.2
5.8
5.4
5.0
pH CURVE
WEEKS 2 4 6 8 10 12 14 16
Gms.
2.0
1.5
1.0
.5
0
GROWTH CURVE
WEEKS 2 4 6 8 10 12 14 16
Gms.
.021
.017
.013
.009
.005
AMMONIA CURVE
WEEKS 2 4 6 8 10 12 14 16
Gms.
.20
.15
.10
.05
0
Cu REDUCTION CURVE
WEEKS 2 4 6 8 10 12 14 16
Gms.
.032
.029
.026
.023
.020
P2O5 CURVE
WEEKS 2 4 6 8 10 12 14 16

method of Folin and Wu (6). Five cubic centimetres of the medium were treated with 2.5 cc. of 10 per cent sodium-tungstate solution and 2.5 cc. of 0.66 N sulphuric acid. Aliquot 2-cc. fractions of this filtrate were used in the determination, and the total amount of copper reduced per bottle was estimated by multiplying the determined value for the aliquot by 250. From this factor sugar was determined by calculation.

6: Coagulable Protein: The relative quantity of coagulated protein formed in each flask as a result of heating for one hour at 60° was noted. However, no quantitative measurement was made of this factor and no attempt was made to determine how much coagulation would have taken place if the hydrogen-ion concentration had been kept uniform in the various flasks.

7: Color Reactions: The protein-free tungstic-acid filtrates, prepared as described above for determination of reducing substances, were tested for the development of blue color with the Folin (7) phosphotungstic-acid color reagent. The procedure was as follows: Two cubic centimetres of the tungstic-acid filtrate were treated with 0.5 cc. of the phosphotungstic-acid solution and 1.5 cc. of the sodium-carbonate solution. The intensity of the blue color produced by the application of this test is indicated in the table below.

A complete record of the analytical data is presented in table 1. A graphic representation of the significance of certain facts revealed by this analytical study is given in the accompanying charts.

Discussion of the Charts: The graphs clearly show the marked changes in the rate of growth of the tubercle bacilli, and in the composition of the medium occurring during the fourth week of growth. In accordance with the observations of Weinzirl and Knapton (8) and others (9), luxuriant growth was accompanied by a rapid production of acidity. The increasing acidity was accentuated by a decrease in the amount of ammonia held in inorganic combination; the decrease in available P_2O_5 was by no means equivalent to the decrease in ammonia. The fourth week of growth was further characterized by the first appearance in analytical quantity of reducing substances other than proteins, the first appearance of blue color with Folin's reagent, and the first appearance of appreciable quantities of a heat-coagulable protein flocculating at 60°. It is quite apparent from the analytical data that during the fourth week of growth a distinct alteration in the structure and composition of the bacterial cell begins to take place.

From the fourth through the eighth week the variations in growth and alterations in medium are less noticeable. The small increase in P_2O_5 is probably due to small amounts of protein present in the medium. The largest weight of dried bacilli was obtained after six weeks' growth. An average yield of about 2 gm. of dry bacilli from 200 cc. of medium after six weeks' incubation was estimated by Anderson (10) of this laboratory during his recent study based on a resource of 2200 cultures grown on Long's medium.

That the rate of cell autolysis was exceeding the rate of growth in the later stages of incubation is indicated by the analytical results obtained for the twelfth week. By the sixteenth week autolysis had effectively cut down the yield of dry bacilli, having decreased the production by 30 per cent as compared with the average weight obtained during the second month. The intensity of coloration with Folin's uric-acid reagent had diminished to such an extent at the end of the sixteenth week that the color had no significance, and, furthermore, the quantity of soluble protein coagulable at 60° was very small.

The increase in the quantity of heat-coagulable protein did not directly parallel the increase in the rate of growth of the bacteria. Slight coagulation was noticed the third week with a small increase for the fourth week. The cultures after the fifth week showed nearly five times as much coagulation at 60° as that observed for the fourth week, despite the small change in pH from 5.6 to 5.4. No attempt was made to demonstrate the first appearance of soluble protein because of the difficulties already noted by Seibert and Long (11). However, it was observed that a light pink coloration was obtained with Millon's reagent after two weeks' incubation, whereas the uninoculated medium gave a negative Millon's reaction. Very little change in the amount of coagulated protein was noted from the fourth week through the eighth.

The measurements of the changing pH of the medium show, in the initial increase in alkalinity and a final persistent acidity, certain differences from the observations made by Weinzirl and Knapton. The synthetic medium of Long's was used in both investigations, but Weinzirl and Knapton reported the addition of a further 5 per cent of glycerol. Since it is well known that the production of acidity is associated with the presence of glycerol, the variations which occur in the two pH curves may be dependent on the different quantities of glycerol incorporated in the medium. The destruction of glycerol with generation of acid

would depress the alkalinity; and the same result would be obtained if an acceleration of growth with concomitant acid production were caused by adding glycerol.

Ten months later, determinations of the pH of the media representing five, six, and seven weeks' incubation showed that no change in this factor had taken place. It was also found that very little or no change had occurred in the amount of reducing substance present.

At this time a portion of the medium representing seven weeks' incubation was freed from protein by a tungstic-acid precipitation, and the protein-free filtrate was hydrolyzed at 90°–100° with a small quantity of concentrated sulphuric acid. The neutralized hydrolysate had a reduction value equivalent to 3.63 mgm. of copper per 2 cc. of the medium as compared with 1.62 mgm. of copper per 2 cc. before hydrolysis.

The increasing alkalinity during the first three weeks of incubation was paralleled by an increase in ammonia probably coming from the amide nitrogen of asparagin (12).

We have thus far made no attempt to determine the nature of the reducing substances formed in the culture medium. Ohnawa (13) claims that glucose is synthesized by the microörganism during growth. In our work no reducing substances were detected by the Shaffer-Hartmann method until the cultures had been incubated for four weeks. When once produced the quantities were small, but the formation of these substances is of great importance in the light of the present general interest in bacterial compounds of a carbohydrate nature. A non-reducing polysaccharide has already been isolated by Mueller (14) from a synthetic medium in which tubercle bacilli had grown. This combination obtained by Mueller is possibly identical with the polysaccharide combination described by Laidlaw and Dudley (15) and separated from tubercle bacilli along with glycogen.

The study of this reducing substance formed during the growth of tubercle bacilli on synthetic media will receive further attention in this laboratory in the near future.

While no method has been developed for distinguishing the products of metabolism from the products of cell autolysis, it seems very evident to the writers that autolysis proceeds much more rapidly as the incubation period of tubercle bacilli is prolonged. It seems very probable to us that the age of the culture may be significant in considering not only the chemical results obtained in the study of the tubercle-bacillus cell, but also in the study of tuberculin found in the medium (16).

SUMMARY

1. The period of increasing growth of human tubercle bacilli (H37) on synthetic medium is characterized by continued changes in inorganic ammonia content and in the pH of the medium.

2. When growth of the bacteria ceases, or the rate of growth is apparently balanced by the rate of cell autolysis, the pH and ammonia values become comparatively constant.

3. The use of protein-free synthetic media of known composition for bacterial growth has enabled us to eliminate the ordinary complications arising from ammonia and amines formed as a result of enzymatic digestion of proteins.

4. The experimental data indicate that there is a correlation between reaction changes and growth of bacilli, and the pH curves obtained by Frothingham (17), Weinzirl and Knapton (8), and by us are in close agreement.

5. The sudden change in pH at the end of four weeks' growth is concomitant with the appearance of reducing substances (sugars?) and coagulable protein in the medium.

6. The growth of tubercle bacilli on Long's medium reached a maximum during the sixth week of incubation.

7. It remains to be determined whether the intensity of color formation with Folin's uric-acid reagent actually characterizes the growth of other bacterial organisms as has been observed in the case of tubercle bacillus H37.

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THE LIPOID PHOSPHORUS-CHOLESTEROL RATIO BEFORE AND AFTER FEEDING RADIATED EGGS TO TUBERCULOSIS PATIENTS[1]

DUNCAN F. McRAE AND THORSTEN INGVALDSON

Steinbock (1) and Hess (2) have shown that vitamine D is produced when impure choesterol and other lipoid mixtures are exposed to utraviolet light. As vitamine D causes calcification in rickets we may conclude that it should act likewise in tuberculosis.

McLewis (3), discussing the factors concerned with the permeability of cancerous cells, states that cholesterol tends to produce a lipoid-continuous phase while lecithin tends to make water the continuous phase; hence, lecithins should increase the permeability of all substances soluble in water but insoluble in lipoids, while cholesterol should do the reverse. This should have a bearing not only on the amount of calcium and phosphates gaining access to tuberculous lesions but also on the amount of toxic substances absorbed from the lesions.

TABLE 1

CASE NUMBER	NUMBER OF EGGS DAILY	WEIGHT OF PATIENT		LIPOID PHOSPHORUS		CHOLESTEROL		RATIO OF PHOSPHORUS TO CHOLESTEROL	
		Before	After	Before	After	Before	After	Before	After
		pounds	*pounds*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*		
1	3	104	110½	8.3	8.5	168	190	1:20	1:22
2	3	126	123	9.5	9.6	200	190	1:21	1:20
3	3	130½	136	11.0	12.5	290	241	1:26	1:19
4*	3	133	131	8.1	8.0	149	137	1:18	1:17
5*	3	151	154	9.2	10.0	180	185	1:19.5	1:18.5

* Controls fed nonradiated eggs.

It was decided to test whether radiated lipoids have any influence on the clinical course of tuberculosis and, if so, whether such influence is due to a change in the lecithin-cholesterol ratio. Yolks of eggs were radiated in thin layers, with continuous stirring for one-half hour at a

[1] From the laboratory of the Manitoba Sanatorium, Ninette, Manitoba.

distance of 16 inches from a mercury-quartz lamp. Patients were then fed these eggs, in the form of egg-nogs, for six weeks.

The lipoid phosphorus and cholesterol were determined in the patients' plasma by Bloor's method (4) before and after feeding. The ratio was then calculated.

The results (table 1) show that there was no change in the ratio and that it remains within the normal limits given by V. Meyer in his table of normal blood constituents.

As far as the lecithin-cholesterol ratio is concerned, the results are entirely negative, and the clinical improvement noted could not be attributed to a shift in circulating lipoids.

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STUDIES ON ACID-FAST MICROÖRGANISMS[1,2]

I. THE REACTIONS OF THE WHITE BLOOD CELLS OF THE RABBIT FOLLOWING INOCULATION WITH LEPROSY BACILLI

EDGAR JONES[3] AND W. O. TIRRILL, JR.

The study of experimental tuberculosis during the last forty years has established the fact that there is a very considerable variation, both in the susceptibility and in the resistance of different species of animals, and of different individuals in any single species, to the infection; and it is quite obvious that the analysis of the factors underlying these differences is of the utmost importance.

As a result of the observations of Cunningham, Sabin, Sugiyama and Kindwall (8) on the reactions of the white blood cells in experimental tuberculosis of the rabbit, interest has been renewed in the possibility of measuring susceptibility and resistance by variations in these cells. The further studies of Baldwin, Petroff and Gardner (1), Cunningham and Tompkins (10) (11), Cunningham, Tompkins, *et al.* (12), Doan and Sabin (13) (14), Dworski, Smith and Gardner (18), and Sabin and Doan (30) (31) (32) have definitely established the importance of the monocytes and lymphocytes as an index of the presence and progress of tuberculous infection.

With these facts in mind, it was clear that much important information might be obtained by the analysis of the reactions of animals when inoculated with other microörganisms of the acid-fast group, particularly with regard to the relationships between the changes in blood and tissues and the pathogenicity of the microörganism employed.

The microörganism chosen for study was the leprosy bacillus. This is one of the chromogenic acid-fast bacilli, growing profusely on ordinary bacteriological media, and belonging to the group isolated by Clegg (5),

[1] From the Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee.

[2] These studies have been assisted by a grant from the National Tuberculosis Association to Dr. R. S. Cunningham.

[3] Mr. Jones's participation in this work was made possible by a grant from the Henry Strong Denison Research Foundation.

Rost and Williams (28) and Duval (16). For a discussion of the pathogenicity of these bacteria and their relationship to the etiological agent of human leprosy, the reader is referred to Duval (15), Kedrowski (19), and Rogers and Muir (27). That these acid-fast strains do cause lesions in animals has been shown by Duval (15), Kedrowski (19), Bayon (2) and others, but, in general, the descriptions have been meagre and have uniformly failed to give any findings regarding the blood. The animals used have varied quite widely, including various "cold blooded" types by Couret (6) and the usual laboratory animals by Duval (15), Duval and Harris (17) and others. These experiments have in common the same findings, that is, that animals are difficult to infect but that proliferative lesions may develop if the doses are sufficiently large and repeated at short enough intervals. Duval and Harris point out that any saprophyte may produce lesions, and Bayon has produced lesions with both the smegma bacillus and the timothy bacillus in rabbits. In general, however, it seems that laboratory animals have a relatively high resistance to infection with acid-fast microörganisms other than tubercle bacilli, since "infections" with the lepra, smegma and timothy bacilli have been both difficult to produce and relatively mild. The resulting lesions have been characterized by the presence of cells of the epithelioid type, many of which have contained the germs used to produce the "infection."

Although no report has been found of the blood findings in experimental studies with leprosy bacilli, there have been numerous reports concerning the blood picture in cases of human infection; and, since Cunningham and Tompkins have shown that the changes in the blood cells in tuberculosis in the human being are quite similar to those in rabbits, it seems worth while to review briefly the reports on cases of leprosy in the human being because of their possible bearing on the experimental findings to be reported here. Moreira (24) found an increase in the mononuclear types in 25 of the 35 cases which he studied. In many of these cases there was a marked eosinophilia, especially in those which had pemphigus. The fluid from the pemphigoid lesions contained numerous eosinophiles. Moreira found no increase in the total number of white blood cells.

Migliorini (22) observed an increase in the total white blood cells, in the eosinophiles and in the lymphocytes, a relatively normal count of large mononuclears, and a decrease in the neutrophiles. The highest

count obtained for large mononuclears in his 4 cases was 9.2 per cent, that of lymphocytes 60 per cent, for eosinophiles 9.6 per cent, and for neutrophiles 55 per cent.

Bourret (3) studied 19 cases, and found the eosinophiles elevated in 16 (in one as high as 29.36 per cent), but he remarks especially that he made no examinations for parasites. The lymphocytes, both large and small, were elevated to a maximum of 54 per cent. The large mononuclears were "up to normal in only two cases." Leger and Marcel (21) report 28 cases, with a careful study of the differential counts of the white blood cells, but they did not give total counts. They found great variability in the eosinophiles, and suggest that the higher counts may have resulted from intestinal parasites. The eosinophiles were elevated (3 to 16 per cent) in 8 cases, present (1 to 2 per cent) in 16 cases, and absent in 14 cases. The polymorphonuclear neutrophiles varied from 44 to 77 per cent and averaged 63 per cent in the 38 cases. The lymphocytes varied between 6 and 37 per cent and averaged 25 per cent. The large mononuclears varied between 1 and 30 per cent and averaged 11 per cent; 21 cases had above 8 per cent and 12 above 15 per cent. The transitional cells were absent in 21 cases, 11 cases showed 1 per cent, 5 cases showed 2 per cent, and 1 case 3 per cent. Thus their evidence indicates that the large mononuclear group is generally elevated in a definite percentage of the cases. Leger and Marcel give no description of their methods of differential analysis between the large mononuclears and transitionals, but they found practically all of the increase to be in the former group. In analyzing the cases into clinical types, they listed 20 cases as of the nervous type, 15 of the tuberculous type and 3 of the mixed type. In studying their table it is wholly obvious that all of the higher values for the large mononuclears occurred in the nervous group, averaging 17 per cent, while in the cases of tuberculous and mixed types these cells averaged 4 per cent. The same thing holds true for the transitionals. In the 15 cases of the tuberculous type there were no counts above 1 per cent, and there were only 2 cases with even this number. On the other hand, Leger and Marcel found that the eosinophiles were elevated only in the tuberculous type.

Lagane and Colombier (20) report 8 cases in which there occurred marked variations of the total leucocytes (4,800 to 18,000), a moderate elevation in the eosinophiles, and an increase in the mononuclears. It is difficult to evaluate these figures as they found lymphocytes averaging 4 per cent, "mononucleaires" 25 per cent, and "grands mononucleaires" 10

per cent. They give no description of these cells, and indicate that they regard the increase in mononuclear elements unimportant. If one considers the total average of these three classes of mononuclear cells, it is obvious that there was but little variation from the normal. The change from the customary normal blood which occurred in these cases was evidently in a shift between lymphocytes and monocytes. Such a shift might represent a real modification in the blood picture or might be the result of a technical interpretation of the various types of mononuclear cells.

Pringault (26) reports 4 cases but divides his mononuclear cells into four groups, making it difficult to appraise his results. He found that the "lymphocytes vrais (petits et grands)" averaged 9.5 per cent, the "lymphocytes leucocytoïdes" 6.25 per cent, the "lympho-leucocytoïdes" 8.5 per cent and the "types de transition" 4.5 per cent, making a total of 28.75 per cent of mononuclear cells. In his conclusions he does not indicate any opinion that these figures are high for any of the cells of the mononuclear group.

Leger and Marcel quote Cabal de Lima as finding that the lymphocytes were elevated in 23 out of 25 cases and the large mononuclears in 16 cases. They also quote Winiartsky as finding the mononuclears increased in 19 cases.

From this brief review of the literature it is quite obvious that the findings which have been most often noted in the blood in leprosy are the elevations of eosinophiles and mononuclears. Despite the possibility of parasitic infections, which might easily have been the cause in many instances of the eosinophilia, nevertheless the uniformity of the finding makes the etiological relation to leprosy quite probable. There is great variation in the type of mononuclear cells which have been found to be increased. It is quite possible to interpret these findings as representing increases in the intermediate and large lymphocytes or as an increase in the monocytes (that is, the large mononuclear type). Since the various classes into which the mononuclear leucocytes have been divided in these studies have not been accurately defined technically, it remains an open question as to whether the so called "large mononuclears," "lympholeucocytes," etc., were monocytes or lymphocytes. The most likely solution is that these cells were in some cases lymphocytes, and in others monocytes, and that there was definite variation in both types of cells, depending upon the type and condition of the case.

METHODS AND MATERIALS

The rabbit was selected for the experimental animal, both because of its ready adaptation to such purposes and because it was thought that a better comparison could be obtained with the work of Cunningham, Sabin, Sugiyama and Kindwall upon experimental tuberculosis in rabbits. Only male animals were used. The microörganism used was the leprosy bacillus *365*, obtained from the Hygienic Laboratories in Washington, D. C. The germs were grown routinely on Petroff egg medium and the cultures used for inoculation were from four to six days old. A very luxuriant growth was obtained, and no difficulty was found in keeping the cultures in an active and healthy condition. The methods of preparation and inoculation were those customarily used for tubercle bacilli and will only be mentioned here very briefly. The growths of bacilli were removed from the surface of the culture with a platinum spade and transferred to a sterile mortar, in which they were ground for five minutes with a very small amount of sterile salt solution. Salt solution was added drop by drop until the required amount of suspension was obtained. This was filtered through sterile cotton, and then centrifugated until a uniform suspension having the desired number of bacilli was obtained. The first inoculations were carried out with a suspension having approximately fifteen bacilli to the oil-immersion field when measured with a standard loop on a square-centimetre slide: 2 cc. of this suspension (the amount of the first injection) contained approximately 40 million bacilli. The second, third and fourth doses were progressively increased, the fourth inoculation consisting of approximately two complete cultures. The largest was estimated at about 12 hundred million bacilli. Each animal received four inoculations at intervals of from 2 to 4 weeks, and all were made intravenously. The differential counts were made on neutral-red films prepared as described in the various publications of Sabin and Cunningham. It is quite certain that while this so called supravital method may not offer any greater advantages for many purposes than the methods of fixed preparations, nevertheless the monocyte group can be much more definitely determined and fewer of these cells are wrongly classified in making the counts than in any method hitherto described. In addition, it is quite obvious that qualitative changes, representing physiological modifications or pathological degenerations, can be more easily observed in cells which are studied in the living state. The differential counts were made under as nearly similar

conditions as possible, and 200 or more cells were counted in each differential. Total white blood cell counts were made with the same pipettes and the same counting chamber; Turck's solution was used throughout. Daily studies were made for a considerable period of time following each inoculation, and later were made at increasing intervals. All supravital counts were carried out in a warm box, the temperature of which was maintained at approximately 38.5°C.

RESULTS

In comparison with the definite changes found both in experimental tuberculosis and tuberculosis in the human being, these experiments have proved essentially negative. Nevertheless, there were certain temporary modifications in the leucocytic formula which seem both interesting and suggestive.

The findings in regard to the white blood cells are given in five charts. Each chart represents a single animal, and gives the total number of white blood cells, of polymorphonuclear neutrophiles, of lymphocytes and of monocytes.[4] Since no consistent findings were obtained with regard to the different types of lymphocytes these have not been charted separately. The eosinophiles have been consistently very low or absent, except in one animal, and this will be discussed in detail later. The basophilic leucocytes have been omitted, as they did not show any deviation from the normal.

On examining these charts, it immediately becomes evident that there was no increase in the level of the total white blood cells following the inauguration of the experimental procedures. In fact, in experiments 1 and 2 there was a mild leucopenia, while the others remained quite normal. But, in studying the changes which took place in the individual types of cells, it is evident that there were certain rather definite results. In the first place, there were several sharp rises in the polymorphonuclear neutrophiles, but these elevations were quite irregular. The curves of the lymphocytes and monocytes, on the other hand, were consistent throughout the series, showing a definite and prompt rise following each exhibition of microörganisms, but returning quite promptly to the normal level. In no animal did either of these types show a postinoculation rise sufficiently sustained to indicate definite anatomical lesions.

[4] In making the charts, the total numbers of cells are given instead of percentages, as it has become evident that this procedure permits of a more accurate analysis of the blood-stream at a given moment.

The polymorphonuclear neutrophiles did not show any consistent change, the marked individual variations being, in all probability, the result of some extraneous conditions. In rabbit 1 (chart 1) there was a marked elevation at the time of the fourth inoculation, but it must be noted that this rise began *before* the inoculation and returned to normal soon after it. The animal, when sacrificed, was apparently quite well, and showed no evidence of any acute inflammatory or other condition that might indicate a definite reaction to the leprosy bacilli. The poly-

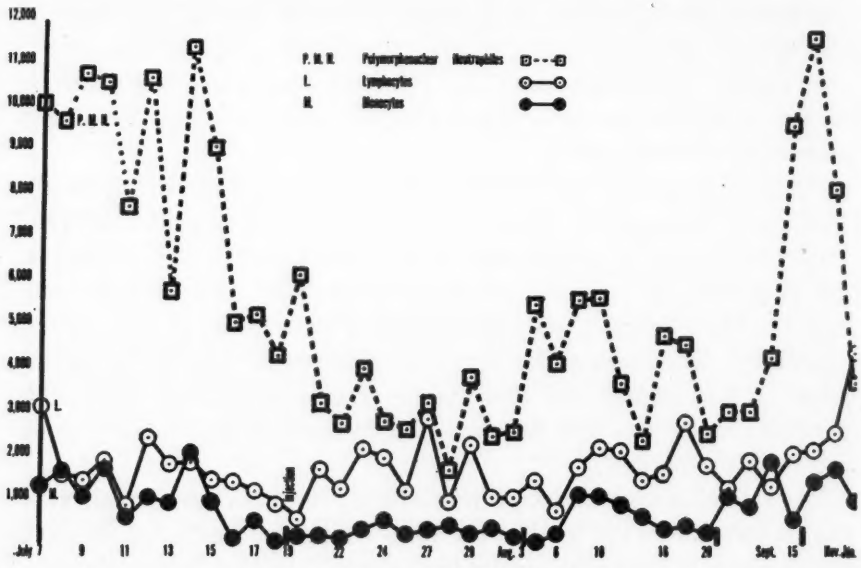

CHART 1

Curves showing the polymorphonuclear neutrophiles, lymphocytes and monocytes of the peripheral blood of rabbit 1

morphonuclear neutrophiles showed a moderate reduction following the first inoculation of bacilli in rabbit 2 (chart 2). In this animal these cells did not, at any time, return to the original high level. This animal was killed because of skin lesions, which were thought to be the result of fighting, but which, taken with the definite increase in the lymphocytes and monocytes, seemed suggestive. The skin lesions, on section, showed no proliferative changes, but nevertheless this was the only animal having any pathological changes characteristic of leprosy (see below). In rabbit 4 (chart 3), a single marked elevation of polymorph-

onuclear neutrophiles occurred just previous to the fourth inoculation. A similar reaction was observed in rabbit 5 (chart 4), where there was a moderate elevation at the same time. These changes must have been the result of an intercurrent infection, since they came just before the inoculation with the leprosy bacilli and since no similar change was noted at any other time. Finally, rabbit 6 was killed during an elevation of the polymorphonuclear neutrophiles, which resulted from an acute pneumonic process (as shown at autopsy), and a single count, taken when it was discovered that the animal was ill, revealed a sharp elevation

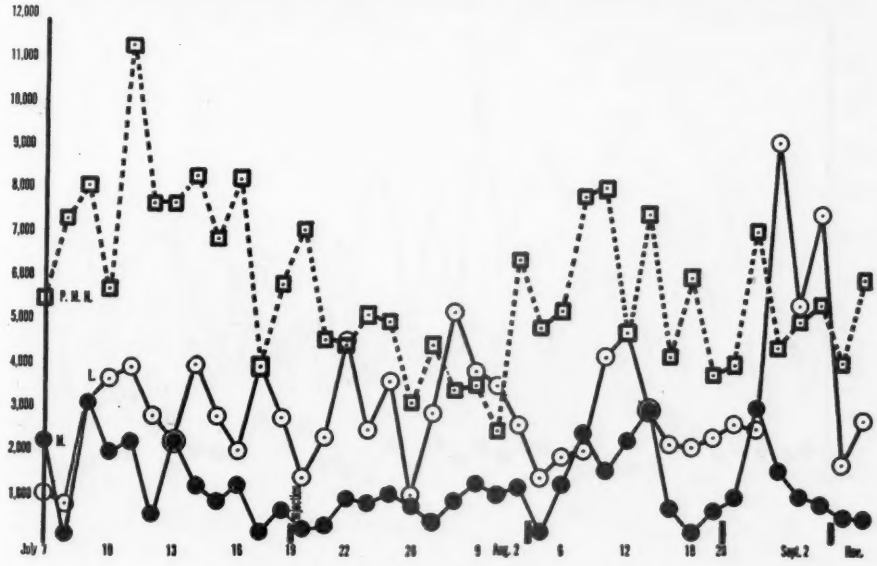

CHART 2

Curves showing data from blood of rabbit 2

in these cells. This animal, at autopsy, presented negative findings, except for an acute pneumonic process in the left lung.

The curves showing the numbers of the lymphocytes and monocytes during the course of the experiments are quite uniform and, as has been stated, show acute increases in both types of cells following the inoculations, with return to normal at the end of a short period of time, usually within ten days. In rabbit 1 (chart 1) the monocytes did not, at any time, exceed the number present before the first inoculation, but the prompt rises following the second, third and fourth doses were too similar

to be merely accidental. The lymphocytes also showed quite prompt and regular increases following the inoculations, but did not rise to especially high levels except at the very end of the experiment, when they were elevated beyond the previous limits and without any special parallel effect upon the monocytes. In rabbit, (chart 2) the same types of changes were found. The monocytes were elevated after each inoculation except the last, and in this case there were unfortunately too few counts to permit any conclusion. The lymphocytes, however, showed a progressively increasing series of elevations following the inoculations.

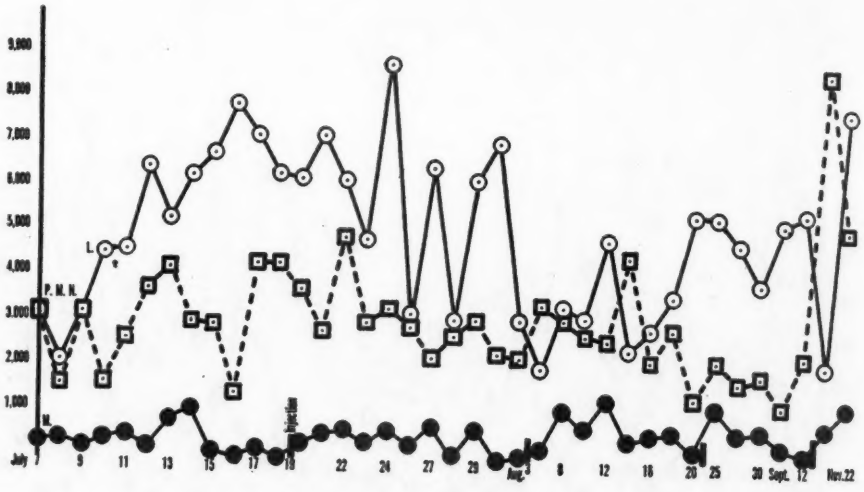

CHART 3

Curves showing data from blood of rabbit 4

In rabbit 4 (chart 3) the monocytes reacted much less markedly to the microörganisms, but there was nevertheless a definite rise following each inoculation. The lymphocytes were very high throughout and, while they were markedly elevated following each inoculation, these elevations did not have the regularity of duration and amount seen in the other animals of the series. In rabbit 5 (chart 4) there was a single period preceding inoculation when the lymphocytes were elevated to an enormous degree, and, at the same time, the monocytes were slightly increased. Otherwise the animal reacted quite like the others, and showed a regular increase in the number of lymphocytes and monocytes following the inoculation of the bacilli. Rabbit 6 (chart 5) also showed mono-

cytes elevated following the second and third inoculations, and lymphocytes increased after all of them. The last (fourth) inoculation produced a severe reaction, which terminated fatally before any counts could be made.

With regard to the other cells, there were no marked changes in any of the animals, except that the eosinophiles in rabbit 2 were definitely increased and maintained a high level throughout most of the experiment. It is interesting to note that in this animal, at autopsy, the tissues were everywhere markedly infiltrated with eosinophiles. This was the only animal in which there were any lesions that simulated the typical findings

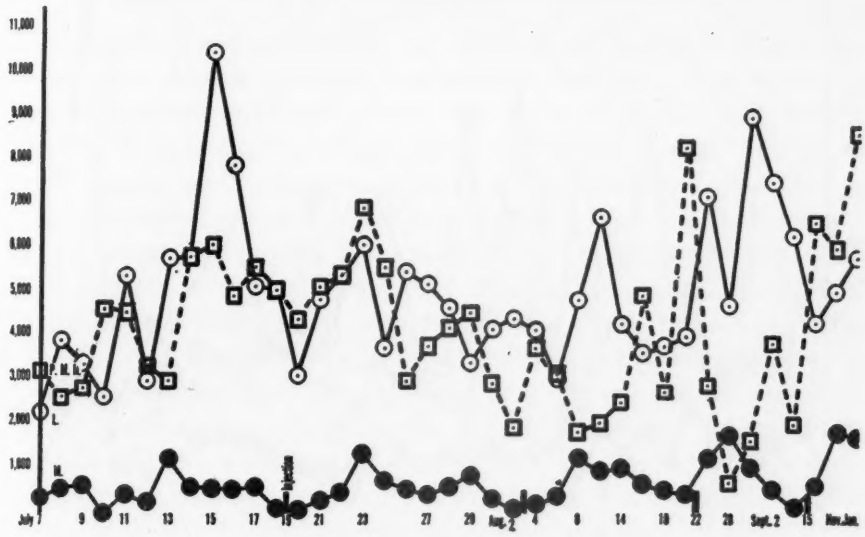

CHART 4

Curves showing data from blood of rabbit 5

in leprosy. The eosinophiles reached 4 per cent, or a total of 460 in this rabbit.

Since it was felt that the specificity of the reaction was one of importance, the experiments being essentially planned for the purpose of comparing the effects of the leprosy bacilli with those of the tubercle bacilli, all the animals were tested for specific agglutinins and were found to agglutinate the strain of leprosy bacilli which had been used, while they did not agglutinate tubercle or smegma bacilli in any dilution. Between the third and fourth inoculations blood was withdrawn from each animal

for agglutination tests. The serum from each rabbit was obtained by centrifugation. Simultaneous agglutination tests were run with the serum of each animal and suspensions of leprosy, tubercle and smegma bacilli. The leprosy bacilli showed agglutination titres of 1:128 in four of the animals and in the fifth animal a titre of 1:256. There was no agglutination of either the tubercle or smegma bacilli at any dilution of the sera. Thus it seems that agglutinins specific for the leprosy bacilli had been developed. These agglutinins were fairly weak, how-

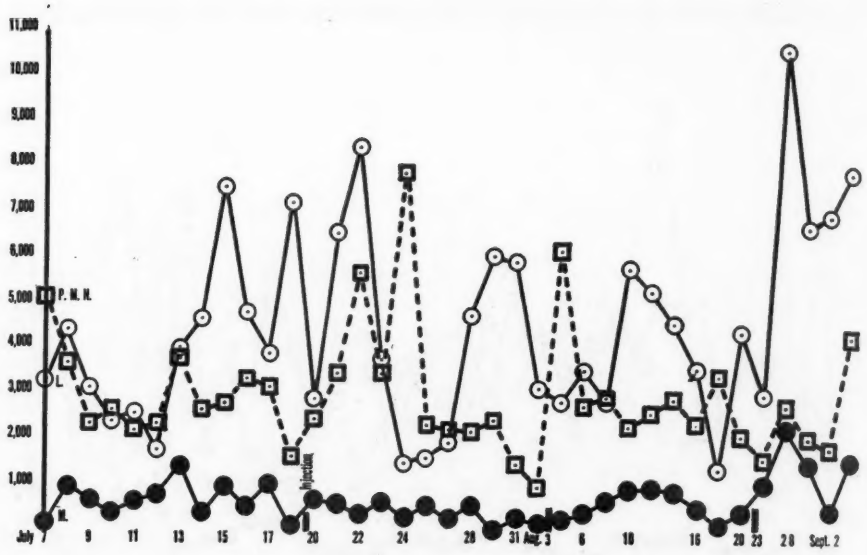

CHART 5

Curves showing data from blood of rabbit 6

ever, since no agglutination occurred in dilutions greater than 1:256 in any case.

Pathological examination revealed changes which were suggestive of an actual infection in only one animal (rabbit 2). In this animal the lungs were infiltrated with large epithelioid-like cells which were often arranged in clumps, but no acid-fast bacilli could be demonstrated within these cells. When studied supravitally, some of these cells were seen to be moderately advanced transitional forms between the monocyte and the epithelioid cell; many were, however, markedly degenerated and filled with globules of fat. Throughout the lungs there were large

numbers of eosinophiles, which were clumped in places and in others scattered widely through the tissues. No giant cells were seen. Similar lesions were seen in the liver, spleen and kidneys; but it is interesting to note that the margins of the skin lesions, already referred to, showed only a mild chronic inflammatory change. None of the other animals showed any changes of this character. Rabbit 5 had an acute pneumonia with no changes elsewhere in the body, and rabbit 6 showed an acute hyperaemic condition in both lungs and a markedly dilated heart, but no changes of a chronic character.

DISCUSSION

There is no more important question from an haematological standpoint than the analysis of the "mechanism of stimulation" of the various types of white blood cells. From the study of clinical cases there is ample evidence that in certain clinical entities the polymorphonuclear neutrophilic leucocytes are selectively elevated, while in others this is true of lymphocytes, and in still others of monocytes. Experimentally, in tuberculosis in rabbits, it has been found that the progressive course of the disease is marked by an increase in monocytes and a decrease in lymphocytes, while during retrogression or recovery there is a definite increase in the lymphocytes. In tuberculosis in the human being the lymphocytes may be either increased or decreased and these changes have been judged to represent the state of resistance. Murphy (25) concludes that experimental elevation of the lymphocytes protects against tuberculosis and cancer. Cunningham and Tompkins suggest that there may be an unknown factor which, when increased, brings about both a greater production of lymphocytes and an increased resistance to tuberculosis. Regardless of the interpretations it seems possible that there is some relation between the number of the lymphocytes and resistance.

A study of the literature on the blood changes in leprosy in the human being indicates that there is a definite increase in the total number of the mononuclear elements of the blood. An analysis of these counts shows that they are possible of several interpretations, owing to the lack of careful description of the cells included under the various groups. The most likely interpretation is that in some cases the lymphocytes were elevated and in others the monocytes. In the experiments reported

above, in which the evidence was strongly against any definite *infection* of the animals, the findings indicated that the leprosy bacilli themselves somehow stimulated the increased production of *both* lymphocytes and monocytes, but only in relatively small numbers. Furthermore, this stimulation was only temporary, and the blood picture returned to normal after repeated temporary rises in both types of cells. These findings suggest that the microörganisms contain within themselves substances which are capable of inducing a temporary increase in both lymphocytes and monocytes. Since the animals, however, did not become definitely infected by the bacteria, it is probable that there was no continued production of either of these substances. This argument indirectly supports the conclusion suggested by Cunningham and Tompkins for the human being, that there is a toxic substance, evolved during the multiplication of the tubercle bacilli, which injures the lymphocytes and therefore the decrease is merely the resultant of the presence of an active infection.

The experiments reported here indicate that the bacilli used (leprosy bacillus 365), when given in large amounts, stimulate the haematopoietic tissues of the rabbit to a temporarily increased production of both lymphocytes and monocytes. It would be interesting to know whether this characteristic is common to all acid-fast microörganisms, and if it is in any degree proportional to their pathogenicity.

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STUDIES ON ACID-FAST MICROÖRGANISMS[1,2]

II. THE REACTIONS OF THE WHITE BLOOD CELLS OF THE RABBIT FOLLOWING INOCULATION WITH SMEGMA BACILLI

LEO SCHWARTZ, JR., AND R. S. CUNNINGHAM

In the first *Study* of this series, Jones and Tirrill (2) called attention to the lack of observations on the cytology of the blood of animals inoculated with so called leprosy bacilli. We have found that there is an almost equal paucity of such observations in regard to those acid-fast bacilli which are found widely distributed in nature but considered relatively nonpathogenic to mammals. There have been many interesting studies on the pathogenicity of these microörganisms, but practically none of this work has included examination of the blood. We selected the smegma bacillus as the next microörganism to study, because of its widespread distribution as a nonpathogenic resident in, or rather on, the human body. It was hoped that there might be some very distinctive characteristics in the reactions of experimental animals to it, and that these would be a guide to the differences in pathogenicity of the smegma and tubercle bacilli.

Of the numerous papers dealing with the lesions produced experimentally by the smegma bacillus, only one has been found that gives any definite analysis of the changes in the white cells of the blood. McJunkin (4) found, after the inoculation of guinea pigs with large numbers of smegma bacilli, that they developed an "endothelial leucocytosis" of from 7 to 10 per cent. In normal guinea pigs he found that the percentage of these cells was less than 1 per cent, so that the change in his experimental animals was evidently a very striking one. Except for this analysis of the percentages of endothelial leucocytes he does not make any statement concerning the differential count of the white blood cells, so that it is difficult to evaluate his results in terms of the classification which we employ. From a consideration of the percentages of these

[1] From the Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee.

[2] These studies have been assisted by a grant from the Research Committee of the National Tuberculosis Association.

cells, it is obvious that McJunkin's endothelial leucocytes can not be regarded as wholly equivalent to the group which we call monocytes, since his animals normally did not show more than 1 to 2 per cent of endothelial leucocytes, while the normal percentage of monocytes in the guinea pig is 7 to 8 per cent [Lyons and Van de Carr (3)]. Whether we may consider the increase in these cells in his experiments to be an indication of change in the group which we call monocytes, is questionable, but, nevertheless, it seems most likely that his endothelial leucocytes are included in, though not equivalent to, the monocytes, and hence his results probably indicate an elevation of this group of cells.

EXPERIMENTAL RESULTS

Our series of experimental animals consisted of 14 rabbits. Two were kept with the inoculated animals as controls. The other twelve were given smegma bacilli in amounts varying from two hundred million to twelve hundred million. In some cases the larger numbers were given to animals which had had previous inoculations, and in others to animals without previous experimental treatment. The culture of smegma bacilli which we used was obtained from the Hygienic Laboratory, Washington, D. C. The method of growth and preparation of the bacillary suspensions were uniform with those described by Jones and Tirrill as used for the leprosy bacilli.

Four rabbits (A. F. 9, 11, 12 and 13) were given two hundred million bacilli intravenously and were studied for a period of approximately three weeks. The monocytes remained entirely normal, both in numbers and in character, throughout the period between the first and second inoculations; the granulocytic leucocytes likewise showed no changes, while the lymphocytes were definitely increased in three of the four animals. In the fourth experiment the lymphocytes maintained an absolutely level course throughout. These changes are illustrated in chart 1 (A. F. 11), which also shows the effect of later inoculations with larger numbers of bacilli. Since none of the four animals which received two hundred million bacilli became sick, they were not killed and therefore no statement can be made concerning possible pathological changes in the tissues.

Three rabbits (A. F. 1, 2 and 3) were given initial inoculations of four hundred million bacilli. In these there were consistent increases in the monocytes, the highest point being approximately twice as high as before

inoculation; the highest points reached before injection were 900, 1,400 and 1,600 respectively, while afterwards the monocytes reached 1,900, 2,400 and 2,400 respectively. Table 1 gives the averages before and

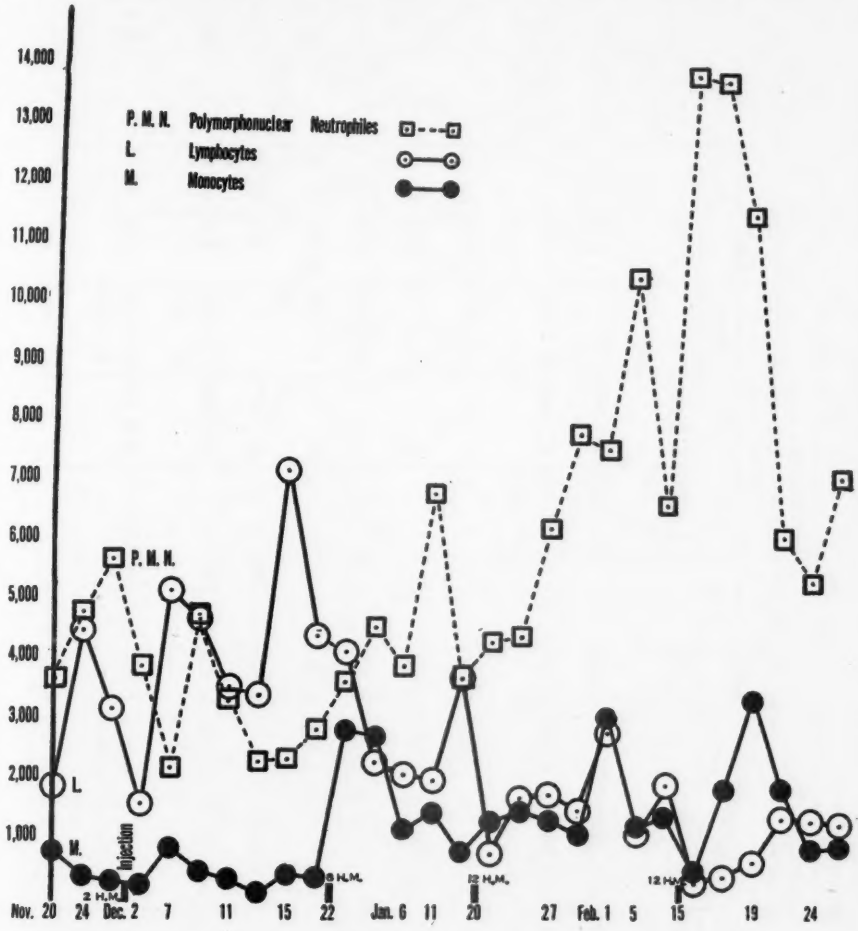

CHART 1

Curves showing the polymorphonuclear neutrophiles, lymphocytes and monocytes of the peripheral blood of rabbit A. F. 11. The numbers of the bacilli inoculated are indicated in hundred millions (h.m.).

after the inoculations, and it is immediately obvious that these rises were sustained, so that the total averages showed even more marked differences. In two of these animals the lymphocytes were moderately elevated, while in the third they maintained approximately their original

TABLE 1

Giving total average numbers of polymorphonuclear neutrophiles, lymphocytes and monocytes before the first inoculation and after each inoculation

The columns are arranged according to the number of bacilli (h.m. = hundred millions), while the letters *A*, *B*, *C*, and *D* refer to the first, second, third and fourth inoculations respectively.

	POLYMORPHONUCLEAR NEUTROPHILES					LYMPHOCYTES					MONOCYTES				
Number	Before	After				Before	After				Before	After			
		2 h.m.	4 h.m.	8 h.m.	12 h.m.		2 h.m.	4 h.m.	8 h.m.	12 h.m.		2 h.m.	4 h.m.	8 h.m.	12 h.m.
1	3,133		A 3,309 B 4,026	C 5,233		3,464		A 2,832 B 1,560	C 1,901		795		A 1,251 B 2,285	C 2,112	
2	3,760		A 6,396	B 5,849		2,528		A 3,370	B 2,652		529		A 1,225	B 1,552	
3	4,130		A 4,448 B 3,287	C 3,966	D 8,625	3,859		A 2,836 B 3,212	C 2,444	D 5,543	970		A 1,390 B 1,894	C 2,104	D 6,143
4	4,624				A 4,966	4,678				A 2,682	723				A 2,454
5	4,468				A 11,172	2,418				A 3,962	523				A 2,162
7	4,320				A 4,143	3,238				A 2,013	726				A 3,590
8	9,257				A 5,399	2,570				A 1,841	1,242				A 2,523
9	2,881	A 2,944		B 4,685		5,243	A 4,505		B 3,890		508	A 454		B 1,502	
11	4,806	A 3,159		B 4,574	C 6,828 D 9,616	3,256	A 4,342		B 2,898	C 1,707 D 914	535	A 448		B 1,858	C 1,601 D 1,570
12	3,381	A 4,388		B 3,840	C 6,225 D 6,452	4,259	A 6,888		B 4,630	C 2,934 D 1,608	534	A 751		B 1,601	C 1,173 D 1,136
13	2,920	A 3,542			B 9,928	4,944	A 4,997			B 876	265	A 551			B 3,796
14	2,160			A 6,718	B 8,220 C 10,143	4,480			A 2,586	B 1,529 C 1,784	240			A 2,497	B 1,815 C 1,545

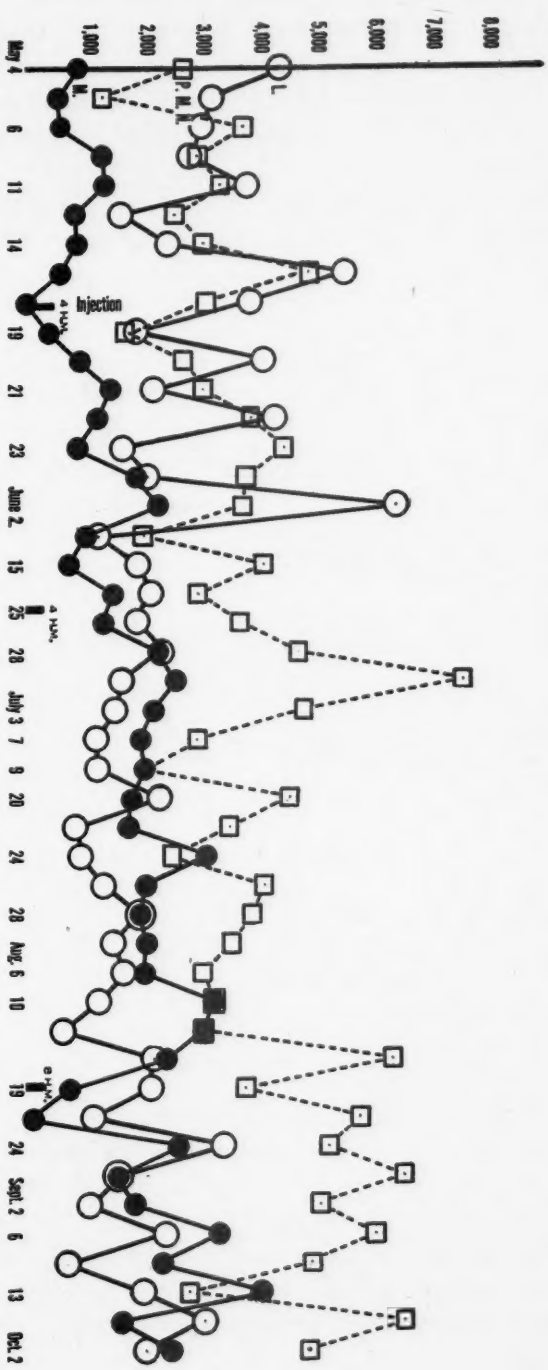

CHART 2

Curves showing data from blood of rabbit A. F. 1

level, although they did not reach quite the same height as they did at one time before inoculation. The polymorphonuclear neutrophiles were quite irregular in their reaction, but showed moderate increases in all three animals. These changes are illustrated in chart 2 (A. F. 1).

Two of these three animals (A. F. 1 and 2) received a second inoculation of four hundred million bacilli, and in both of these there was a second rise in monocytes, one (A. F. 1) reaching a level of 3,200 and the other

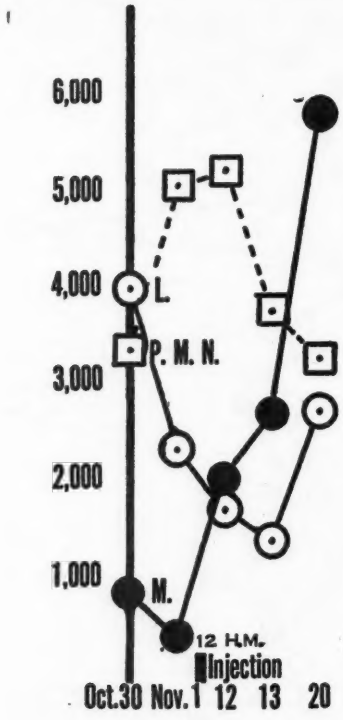

CHART 3

Curves showing data from blood of rabbit A. F. 7

(A. F. 2) 3,400. The monocytes had returned to the normal preinoculation level in one, but not in the other; nevertheless both reached approximately the same new level and after approximately the same length of time (that is, 14 days). In one of these animals, the polymorphonuclear neutrophiles remained at the same level as during the period preceding the second inoculation, while in the others there was a moderate drop. The lymphocytes were moderately reduced in both animals, more so in A. F. 1 (shown in chart 2) than in A. F. 2.

Only one animal (A. F. 14) was given eight hundred million bacilli as an initial inoculation, and in it there was a prompt rise of the monocytes from a level of about 500 to one of 4,000 cells and a progressive decrease to normal in about two weeks' time. The polymorphonuclear neutrophiles showed a very temporary increase of marked degree and then promptly returned to normal, while the lymphocytes fell abruptly from 4,000 to 1,000 and then gradually returned to the previous level during the period in which the monocytes fell.

Seven rabbits (A. F. 1, 2, 3, 9, 11, 12 and 14) received inoculations of eight hundred million bacilli. Of these, two (A. F. 11 and 12, shown in charts 1 and 4 respectively) received two inoculations of this number of bacilli. Following every inoculation of eight hundred million bacilli, the monocytes were elevated, the polymorphonuclear neutrophiles were elevated in all except one (A. F. 1), while the lymphocytes were elevated in only one of the seven (A. F. 1). Both of these exceptions to the reactions occurring in the other animals were noted in the same rabbit (A. F. 1), and this animal also showed the highest level of monocytes, reached after the inoculation of eight hundred million bacilli. These changes are shown in chart 2.

Four rabbits (A. F. 4, 5, 7 and 8) were given twelve hundred million bacilli as a first inoculation and in every case the monocytes were markedly elevated, the maximum reached being 5,900 in rabbit A. F. 7 (chart 3). The polymorphonuclear neutrophiles were increased in one of the rabbits (A. F. 5) and maintained the previous level in the other three. The lymphocytes were reduced in three of the animals, and in the fourth (A. F. 5 in which they had, in the two counts preceding inoculation, fallen to a very low level) they were increased, but did not reach the previous high level. Five rabbits (A. F. 3, 11, 12, 13 and 14) received twelve hundred million bacilli on the second, third or fourth inoculations and again, in every instance, the monocytes were markedly elevated, reaching in one animal (A. F. 3) the highest level of the series, 7,300. The polymorphonuclear neutrophiles were elevated in every instance. The lymphocytes were decreased in three animals, were definitely elevated in one (A. F. 3, coincidental with the highest point reached by the monocytes), and gave an equivocal reaction in one. This last experiment (A. F. 12) was interesting, in that the lymphocytic reaction presented the same characteristics after each inoculation, regardless of the number of microörganisms exhibited. The course of the changes in

the blood of this animal is shown in chart 4. It will be noted that the monocytes showed progressively increasing elevations following the successive inoculations, and the general trend of the curve of the monocytes is seen to be toward a higher level. On the other hand, the lymphocytes showed a general tendency to fall to lower levels through-

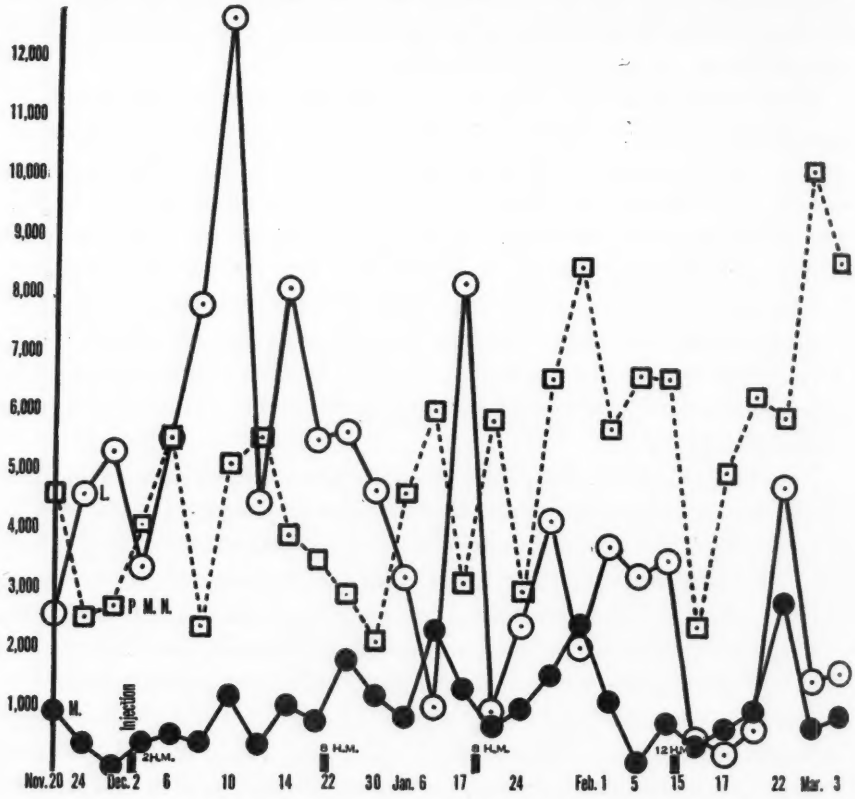

CHART 4

Curves showing data from blood of rabbit A. F. 12

out the course of the experiment, despite the fact that there was a very definite elevation following each inoculation. It is interesting to note, however, that the high peaks of these successive rises in the lymphocytes became less with increased numbers of bacilli, and that in this experiment there was a definite upward trend in the numbers of polymorphonuclear neutrophilic leucocytes.

In analyzing the series of experiments as a whole, certain interesting relationships between numbers of bacilli and numbers of cells could be seen. These have been given in charts 5, 6 and 7, which show the average number of the cells (monocytes, polymorphonuclear neutrophiles and lymphocytes respectively) before injection and following injections of various amounts of bacilli. It is obvious that these generalizations are

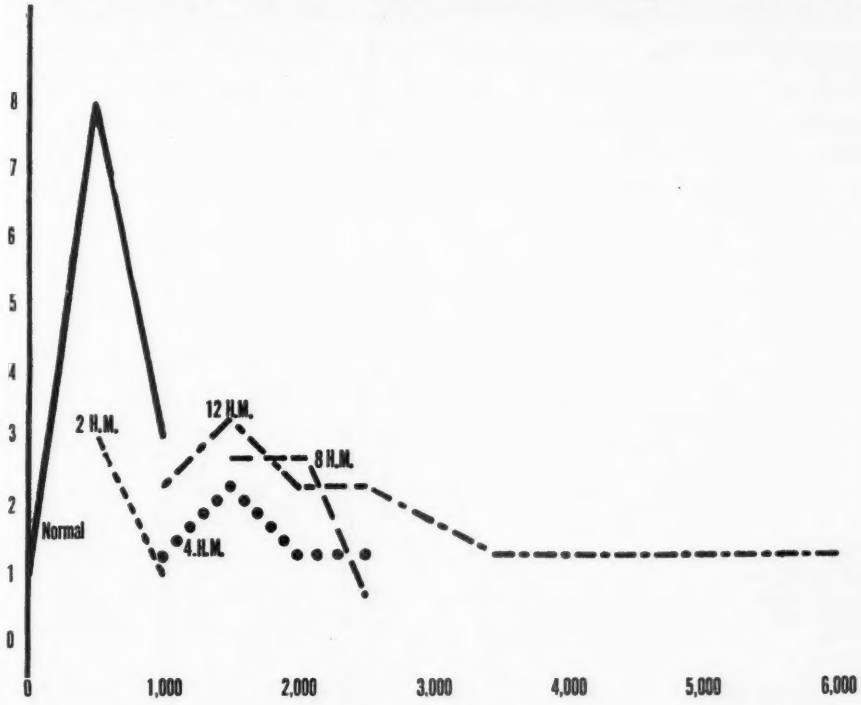

CHART 5

Curves showing distribution of experimental animals with regard to the average number of monocytes before and after inoculations. The animals are grouped according to numbers of bacilli given (indicated as hundreds of millions, h.m.).

based upon the reactions of animals which had had previous inoculations as well as upon those in which the larger numbers of bacilli were given in the first inoculation. There were 14 animals in the series and in each chart the normal preinoculation averages for these are given. The 12 rabbits which were utilized for the experiments received a total of 28 inoculations, and, for the purpose of this analysis, these have been treated as if they were entirely separate experiments. The possible

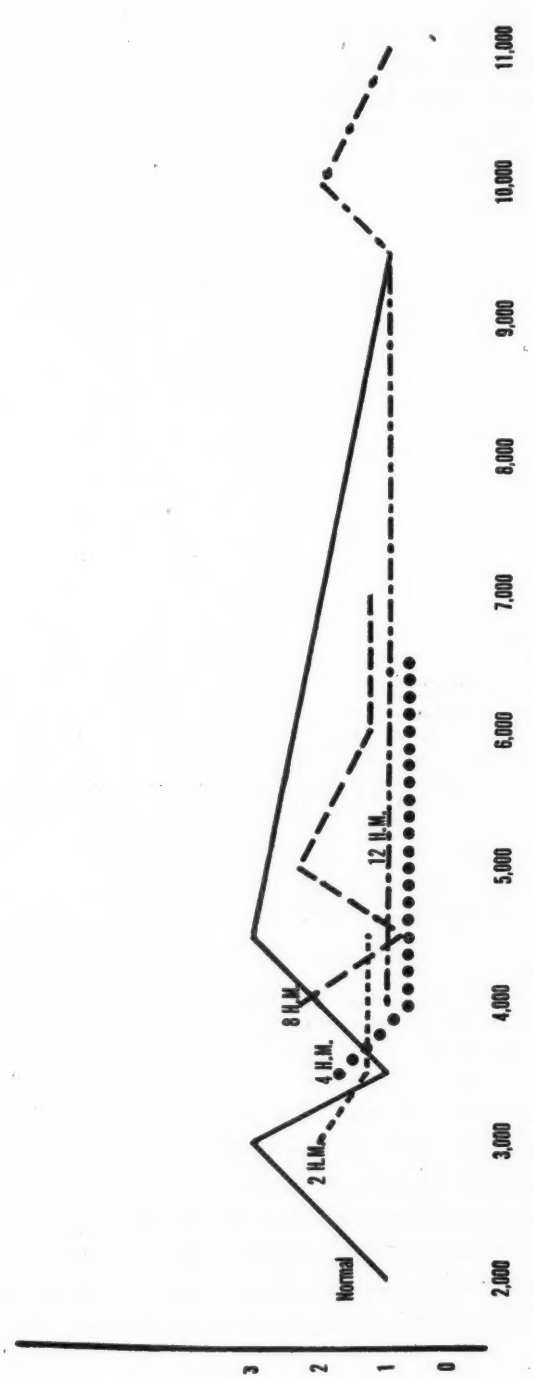

CHART 6

Curves showing distribution of experimental animals with regard to the average number of polymorphonuclear neutrophiles before and after inoculations.

bearing of second, third and fourth inoculations on hypersensitive conditions will be discussed later.

Chart 5 shows the average numbers of monocytes in the 14 rabbits before inoculation and in the 12 rabbits following inoculations of two, four, eight and twelve hundred million of smegma bacilli. In general, it is quite obvious that there was a marked shift of the distribution toward the higher values in terms of cells, with the increase in the number of bacilli given. After the four inoculations of two hundred million bacilli, there was evidently no effect upon the monocytes, as the values fall in the same part of the curve as the normals. After the five inoculations of four hundred million bacilli, only the value of one animal remained within the normal level, and those for the other four moved definitely to the

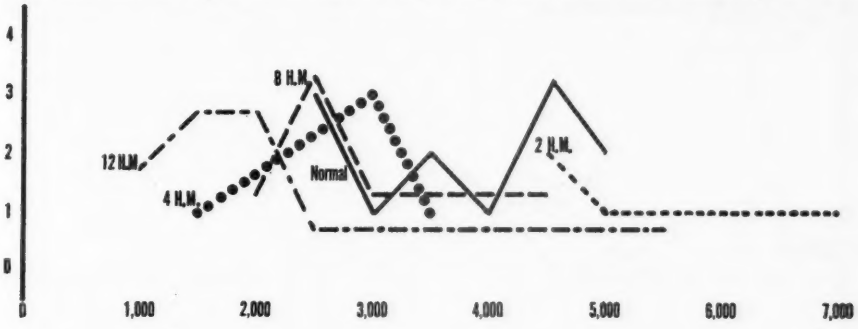

CHART 7

Curves showing distribution of experimental animals with regard to the average number of lymphocytes before and after inoculations.

right. After eight hundred million bacilli there was evidently no very marked shift from the values for the animals which received four hundred million, although the peak of the curve was elevated to a slight degree, since three animals reached a level of 2,000 cells in contrast to one following the injection of four hundred million bacilli. When twelve hundred million bacilli were given there was a very marked shift to the right. It is evident, therefore, that there was a proportionately greater number of monocytes in the circulating blood following the introduction of increasingly large numbers of smegma bacilli.

In chart 6, which shows the average numbers of polymorphonuclear neutrophilic leucocytes following the progressingly increasing numbers of exhibited microörganisms, it is immediately evident that there was a slight shift to the higher values, but this was very minor in amount,

and only reached an appreciable degree in the animals receiving the maximum dose of twelve hundred million.

In the case of the lymphocytes (shown in chart 7) a slightly different result was obtained. It is most interesting to note that following inoculations of two hundred million bacilli, there was a moderate shift of the curves to the right, while with four hundred million and eight hundred million the curves were almost wholly within the normal range. When twelve hundred million bacilli were given, the lymphocytes were moderately reduced, and the curve therefore moved to the left.

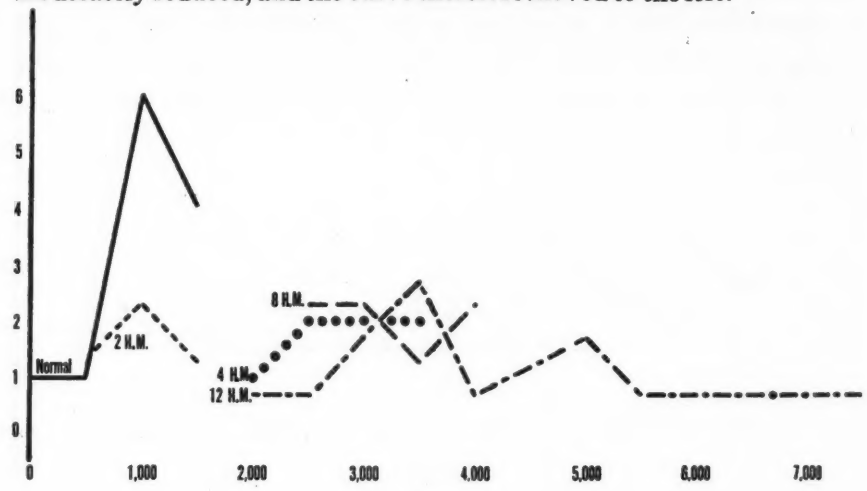

CHART 8

Curves showing distribution of experimental animals with regard to the highest number of monocytes reached before and after inoculations.

Chart 8 is arranged to show the maximum elevations reached by the monocytes following inoculations of the different numbers of microörganisms. This is included because it seems important to consider the extent of the "swing of the pendulum," so to speak. If one remembers that the peak of the curve of any such response represents more exactly the extent of the reaction, while the averages indicate its duration, it is immediately obvious that the changes shown in chart 5 are exaggerated in chart 8. After two hundred million bacilli, the values still remained within the normal limit and after the larger injections there was a progressive shift to the right, which was even more marked than when the average counts were taken. Similar charts for polymorphonuclear neutrophiles and lymphocytes show proportionately the same modification of the reactions

indicated by the average number of cells; these differences, however, are not sufficiently great to necessitate illustration.

It is interesting to note that there was also some relationship between the size of inoculation and the rapidity of response. After inoculation with two hundred million bacilli there was no change noted in the

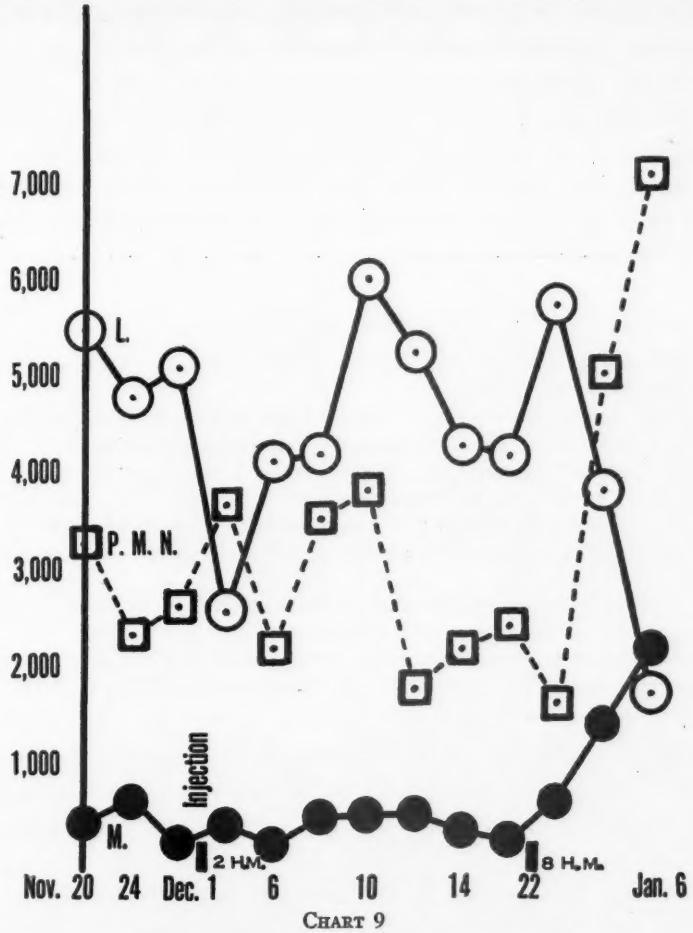

CHART 9

Curves showing data from blood of rabbit A. F. 9

monocytes. After four hundred million they began to rise gradually and the peak was reached at about ten to fourteen days. After eight hundred million the response was somewhat more prompt and a marked elevation occurred from seven to eleven days after the inoculation, while with twelve hundred million bacilli there was a still more prompt re-

sponse, the interval between inoculation and marked rise being from four to ten days. These intervals are only estimates but from a study of charts 1, 2, 3, 4 and 9 the tendency to a more rapid response on the part of the monocytes following increasing numbers of bacilli is immediately apparent. The response of polymorphonuclear neutrophiles and the lymphocytes were both so much less marked, and on the whole so irregular, that no differences could be determined between the size of dose and the time of response.

The findings at autopsy have proved of considerable interest in these 12 animals. They have certain characteristics in common, and in addition fall into groups which are suggestive, when considered in relation to the dosage and blood findings. In 10 of the 12 rabbits which

PLATE 1

Description of Figures

FIG. 1. Photomicrograph of section of lung of rabbit A. F. 4, showing typical giant cells. Haematoxylin and eosin. × 200.

FIG. 2. Photomicrograph of section of liver of rabbit A. F. 8, showing typical giant cells without any marked reaction of surrounding tissues. Haematoxylin and eosin. × 200.

FIG. 3. Photomicrograph of section of lung of rabbit A. F. 1, showing group of tubercle-like structures. Haematoxylin and eosin. × 55.

FIG. 4. Photomicrograph of section of lung of rabbit A. F. 2, showing clump of typical epithelioid cells without very marked reaction of surrounding tissues. Haematoxylin and eosin. × 110.

FIG. 5. Photomicrograph of section of omentum of rabbit A. F. 12, showing invasion of a mass of epithelioid cells by lymphocytes. Haematoxylin and eosin. × 110.

FIG. 6. Photomicrograph of section of omentum of rabbit A. F. 12, showing the replacement of the epithelioid cells by connective tissue. Haematoxylin and eosin. × 110.

were given smegma bacilli, there were definite proliferative changes, which were, in general, quite similar to those seen in tuberculosis, that is, the production of epithelioid and giant cells, and the formation of "tubercles."

In analyzing the experiments into groups, they fall into five catagories depending upon the type and number of inoculations. *I:* Four rabbits (A. F. 4, 5, 7 and 8), each of which received one massive inoculation. *II:* Two rabbits (A. F. 9 and 13), each of which received two inoculations. The second was a massive inoculation which was given about three weeks after the first. *III:* One rabbit (A. F. 2), which received two inoculations, but the second was not given until six weeks after the first. *IV:* Two rabbits (A. F. 1 and 14), each of which received three inocula-

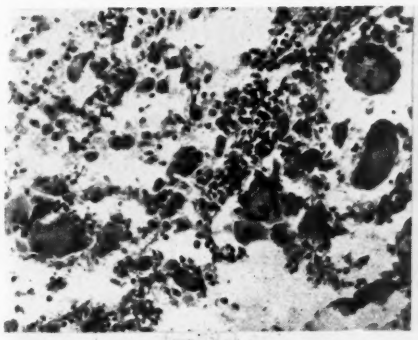

Fig. 1

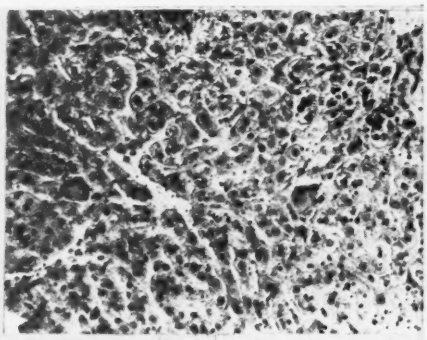

Fig. 2

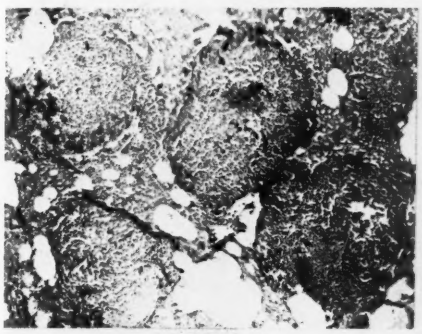

Fig. 3

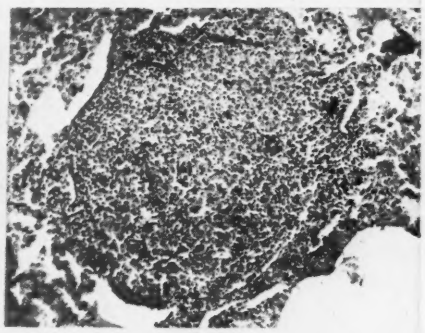

Fig. 4

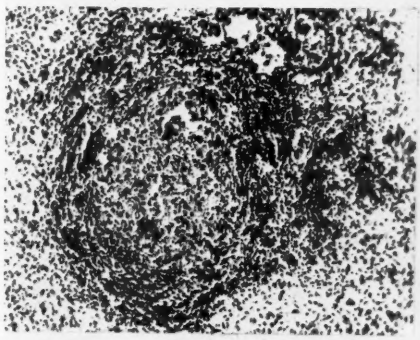

Fig. 5

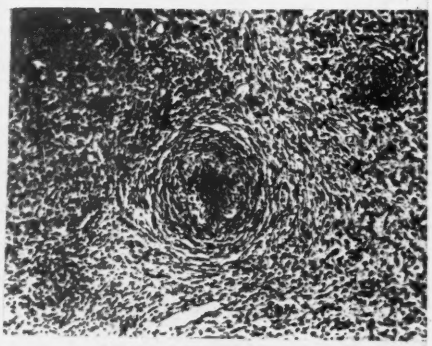

Fig. 6

tions, increasing progressively in amount. *V:* Three rabbits (A. F. 3, 11 and 12), each of which received four inoculations, also in increasing numbers.

The first group of four animals (receiving massive inoculations) all showed quite similar reactions. The monocytes were markedly elevated and remained so until the death of the animal. In one (A. F. 5) the animal died three days after inoculation, and the tissues showed only an acute inflammatory process which was especially marked in the lungs. The blood in this animal showed a marked rise in monocytes and in lymphocytes, but the lymphocytes did not increase beyond the high peaks of the normal level. In the other three animals (A. F. 4, 7 and 8) there was a much more marked rise in monocytes and a coincidental fall in lymphocytes. These animals lived seven, eight and sixteen days respectively, during which time the monocytes continued to rise and the lymphocytes remained at a fairly low level. The most remarkable part of the pathological picture in these three rabbits was the widespread formation of giant cells. Many clumps of epithelioid cells were seen, especially in the lungs and omentum, but the tremendous number of giant cells was quite amazing. In the lungs, these multinucleated elements were found surrounded by masses of epithelioid cells, in the borders of the tubercle-like structures, in the otherwise normal septa, and free in the alveolar spaces. As many as eight to ten could be counted in the average oil-immersion field. Figure 1 is from the lung of rabbit A. F. 4, and shows eight typical giant cells, most of which are free in the tissues. Figure 2 is from rabbit A. F. 8 and shows two giant cells in the liver, without any apparent reaction in the adjacent tissues. These giant cells were found in liver, lung, spleen and omentum in great numbers, but were especially abundant in the lungs. Thus it seemed that, following the large initial injection of these microörganisms, there was a massive reaction toward production of epithelioid cells and giant cells, with very little evidence of any acute inflammatory reaction except in rabbit A. F. 5, which died with evidence of an acute pneumonic infection.

In group II the 2 rabbits received a small inoculation, which produced no noticeable changes in the blood. After twenty-one days both animals received a very large inoculation and died in seven days. Following this inoculation there was a marked fall in lymphocytes and a marked rise both in polymorphonuclear neutrophiles and in monocytes (chart 9). At autopsy these animals showed some production of epithelioid cells,

a few giant cells, and the formation of small nodular masses, but these were much less marked than in the first group, despite the fact that the animals lived about the same length of time after the massive inoculation. There was, however, a very marked oedema of the lungs at autopsy, together with evidence of acute inflammatory processes.

The third group consisted of only one animal (A. F. 2), which received two inoculations, the first of which (two hundred million bacilli) was followed by a moderate rise in both monocytes and lymphocytes. Both types of cells remained elevated throughout a period of six weeks until the second inoculation was given. This second inoculation consisted of eight hundred million bacilli, and was followed by a moderate rise in monocytes, which decreased slightly over a period of a month, but never reached normal, and finally, during the last week, the monocytes were markedly increased (3,200). The lymphocytes, on the other hand, fell consistently throughout the six weeks intervening between the second inoculation and the death of the animal. These cells reached 5,200 at the highest point, following the first inoculation, but fell to 1,800 near the end of the experiment. During the last ten days there was a moderate polymorphonuclear neturophilic leucocytosis. In the tissues there was a generalized production of epithelioid cells and these were usually clumped together, but there was very little necrosis or peripheral tissue reaction. Figure 4 shows such a clump from the lung of this animal (A.F.2). The liver showed marked parenchymatous degeneration. The adrenals were very interesting. Grossly, they were markedly swollen and soft, the central part being very yellow in color. Scrapings contained many cells with cytoplasm loaded with fatty droplets, but showing no vacuoles staining with neutral red. The section shows that the entire medulla and almost half of the cortex have been replaced by large cells with very granular cytoplasm and deeply staining nuclei, looking much like epithelioid cells which had undergone some degenerative process. These cells extended out into the normal cortical material in finger-like processes, which were marked off very exactly, since there was no intermingling of the two types of cells. This reaction was not seen in any other of the animals.

Group IV consisted of two animals, each of which received three inoculations. A. F. 1 was killed during the height of the monocytic reaction (see chart 2) and the tissues were found to contain very marked proliferative changes. The lungs were filled with masses of epithelioid

cells arranged in clumps. There were very few giant cells. There was very little necrosis and no evidence of any acute inflammatory reaction. Figure 3 shows the nodular masses occurring in the lungs. Rabbit A. F. 14 was followed over a longer period of time and was allowed to return to an apparently normal state. At autopsy the only findings were small scattered nodules of epithelioid cells in the lungs and omentum.

Group V consisted of three animals receiving four inoculations each. In rabbits A. F. 11 and 12 (charts 1 and 4 respectively) the general reactions were quite similar. Both were apparently quite normal when sacrificed and both had the same type of pathological changes. There was marked fibrosis of the omentum with many clumps of epithelioid cells, some of which were markedly infiltrated with lymphocytes (figure 5) and others were in various stages of connective-tissue healing (figure 6). There was also marked degeneration of the liver cells which was principally periportal in character. Rabbit A. F. 3 apparently developed an acute infection which complicated the picture; both reactions were quite obvious in the tissues. The lungs were almost solid masses of epithelioid cells surrounded by acute inflammatory areas and widespread necrosis. The liver showed moderate degeneration of the parenchymatous elements, but not so widespread as in the other animals of this group, but there were very large masses of epithelioid cells scattered here and there throughout the organ.

To summarize the findings at autopsy of the entire series, it is clear that one fact stands out as preëminently characteristic, that is, the production of epithelioid cells in the tissues. In some of the animals these cells were grouped in masses while in others they were more or less generally distributed. In the more acute experiments giant cells were very prominent, and of particular interest was the fact that they occurred in the alveolar spaces of the lungs as well as in the septa and in the nodules of epithelioid cells. When studied in fresh preparations the giant cells always contained large numbers of bacilli and fat droplets, and, when they were not especially injured, conformed to the typical picture of the giant cell of tuberculosis as seen in the neutral-red preparations.

The epithelioid cells were quite typical of those seen in tuberculous animals. These have been described and figured by Cunningham, Sabin, Sugiyama and Kindwall (1) and by Sabin and Doan (5). These cells were seen, in many instances, to contain rod-shaped bacilli, which were often surrounded by red vacuoles, although at times these vacuoles were

absent and the bacilli appeared as refractive rods in the cytoplasm. This occurred in all dead cells (when there was no staining supravitally), and in some of the living elements the vacuoles of the cell contrasted sharply with the unstained bacilli. That these structures were bacilli and not long mitochondria, was ruled out by the routine use of Janus-green, which in every case showed the mitochondria as wholly distinct from the rods we considered as being bacilli. As a further control, smears were made from the tissue scrapings (where there were many epithelioid cells) and stained with carbol-fuchsin. In these preparations many acid-fast microörganisms were found, both within the cells and free. Bacilli were found in all of the animals in which there were many epithelioid cells (A. F. 1, 2, 4, 7, 8, 9 and 13), but they were most numerous and more of them were apparently uninjured in the cells in rabbits A. F. 4, 7 and 8, when very large initial injections were given. Many epithelioid cells containing large numbers of fatty droplets were seen in all of the experiments, but these, on the other hand, were more numerous in the chronic animals which finally succumbed with evidence of proliferative changes predominating in the tissues (A. F. 1 and 2). The findings that occurred only in a few of the animals must be regarded as merely suggestive. Two showed oedema of the lungs, six marked degeneration of the liver, and other scattered lesions occurred in several. But the outstanding feature of the tissue examinations was the massive and widespread production of epithelioid cells.

DISCUSSION

The object of the experiments reported here was to determine whether the reactions of rabbits to smegma bacilli had any common factors with those seen after inoculation with virulent tubercle bacilli. The results are categorically definite in showing that there is at least one clear-cut similarity in the two types of infection, that is, the increase in the number of the monocytes of the circulating blood and tissues and the modification of these in the direction of the so called epithelioid cells. That the smegma bacillus is not especially toxic is amply indicated by the long course pursued by some of these animals without any change in the blood counts; but when sufficiently large numbers of microörganisms were injected the animals developed massive lesions of lungs and other tissues and finally died from the effects of the lesions.

The similarity between the reactions of the animals to smegma bacilli and tubercle bacilli is of considerable importance, and indicates that there

is at least some property in common in its reaction to these two microörganisms. From the experiments of Jones and Tirrill it seems probable that this property is not present to such a large extent in leprosy bacilli, since even with the very largest numbers there were no reactions in any way comparable to those obtained from inoculations with smegma bacilli. What this common property is, we do not know, but it seems worthy of further study, inasmuch as it might lead to some assistance in the puzzling questions that are now facing us with regard to the effects which the various chemical fractions of the tubercle bacilli have on the blood and tissues of experimental animals.

A very interesting question was raised by two of the experiments (A. F. 9 and 13), in which there were second injections followed by very prompt and generalized reactions. These reactions have certain aspects, especially the findings in the tissues at autopsy, which are similar to the allergic response in sensitized tuberculous animals. If these reactions prove, on further study, to be allergic in character, it would still further add to the interest in the similarities between the smegma and tubercle bacilli.

In studying the epithelioid cells, it was very interesting to note that while the bacilli had been phagocytized in very large numbers, most of them were surrounded by neutral-red vacuoles, indicating, we think, the beginning degeneration of the bacilli. While there is, as yet, no proof that this assumption is correct, nevertheless the much greater number of bacilli surrounded by activity vacuoles in the case of smegma than was found (Cunningham, Sabin, Sugiyama and Kindwall) in the case of tubercle bacilli must be considered as suggestive.

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THE FOOD PROBLEM IN A SANATORIUM[1,2]

ERNEST S. MARIETTE

With medicine, in the beginning, developing almost as a corollary to dietetics, it is easy to understand how food and diet have come to occupy such an important place in the treatment of a disease so frequently associated with loss of weight. The fact that the diet and food vary with the race, the religion, and the available food supply of each country or section of the country, while tuberculosis prevails throughout the entire world, has not seemed to alter man's opinion about the importance of food in the treatment of tuberculosis. Even as late as 1861 Lawson concluded that, as the diet differed so in each section of the United States, in the north, in the south, in the east and the west, and as tuberculosis occurred throughout the entire country, "no one diet could produce tuberculosis" (1).

I wonder whether we could not now conclude that either there is something fundamentally wrong with the diet of the entire world or else there is something which is present in all countries that is more important than diet in the prevention or treatment of tuberculosis. Seham (2) calls attention to the fact that even though subnormal school children were given extra food at school they did not gain in weight or strength until a rest period was added.

Thus, while diet and food are still part of the "tripod of the treatment" (rest, fresh air and good food) which form the backbone of the sanatorium management of tuberculosis to-day, enlightened opinion no longer considers diet of paramount importance. To-day a well-balanced nutritious diet adapted to the needs and modes of living of the tuberculosis patient is advised rather than any one particular diet, such as the high-protein diet of milk and eggs which was formerly so often prescribed. Many now believe that this diet, unless there is definite gastrointestinal disturbance present, should be the same for the tuberculous as it is for the nontuberculous individual who is living under the same relative conditions of exercise. Thus, a high-caloric diet may be prescribed for a

[1] From the Glen Lake Sanatorium, Oak Terrace, Minnesota.

[2] Presented at the twenty-second meeting of the American Sanatorium Association, Indianapolis, Indiana, May 23, 1927.

man who is free from tuberculosis but below normal weight, and the same high-caloric diet for the consumptive who is also below weight. When the high-caloric diet is prescribed for the consumptive, he should be informed that it is a diet used to increase weight either for those with tuberculosis or without tuberculosis, rather than to cure the tuberculosis. It should also be explained to him that, while a gain in weight will probably increase his resistance to disease in general, he can put on weight without any reparative change in his tuberculous process.

The differentiation of diet along racial, religious, and provincial lines has been handed down from generation to generation until now the average citizen has a mass of personal prejudices and theories concerning his food. This, together with the number of patients and the length of stay of the average patient, makes the food problem of the sanatorium unique. Unlike the hotel, the sanatorium deals with people whose normal physical outlet is curtailed, whose normal interest in the competitive struggle of life is replaced by the one idea to get well, and, in many instances, whose chief occupation is to wonder what is to be served at the next meal. Therefore, the sanatorium must furnish sufficient variety in its dietary schedule to avoid jaded appetites, and, in addition, must deal with people whose gastrointestinal functions are often affected by the poisons of their disease. The proper diets for this latter condition are still disputed and may well be a fertile field for research. However, the pathological aspects are to be disregarded in this paper, and the subject is to be discussed from the point of view of a problem in sanatorium management.[3]

The diet prescribed by the medical department is one of about 3,000 calories per day, including a half-pint of milk at each meal and at bedtime, and containing from 70 to 100 gm. of protein and 300 to 400 gm. of carbohydrate. Those who are below weight receive an extra half-pint of milk morning and afternoon. This diet is well-balanced, nutritious, and varied according to seasons and holidays, and is served in the most attractive and appetizing manner that the physical equipment and budget will permit.

The method outlined below is our dietitian's solution of our food problem.

The menus are prepared for 21 days. This is an arbitrary period of time; 28 days would be as satisfactory, but preferably the period should be made

[3] Those interested are referred to "The Effect of Diet on Experimental Tuberculosis" in *The Newer Knowledge of Nutrition* by McCollum and Simmons.

out for a definite number of weeks, as such a plan enables a week's work to be planned ahead and allows employees definite and regular time off duty. This plan avoids monotony and repetition in the diet, permits cost to be standardized, labor and use of equipment to be equalized, and the less desirable and more desirable foods to be impartially distributed to every unit in the house.

The sanatorium is divided into nine units as shown in figure 1. The horizontal divisions represent the days, and the vertical divisions represent the groups

DINNERS

	PATIENTS					EMPLOYEES			
DAY	EAST	WEST	AD BLDG	PAT D R	SPECIAL	STAFF	NURSES	WOMEN	MEN
Wed 1	Rt lamb	Chicken	Rt lamb	Rt lamb	Bf steak	Bf steak	Liver & bacon	Pot rst	Pot rst
Th. 2	Chicken	Lamb stew	Bf steak	Bf steak	Lambstew	Pk chop	Lambstew	Liver & bacon	Liver & bacon
Fri 3	Fish	Fish	Fish	Fish	Fish	Fish	Fish	Fish	Fish
Sat 4	Bf steak	Pot rst	Pot rst	Pot rst	Pot rst	Chicken	Chicken	Vl cutlet	Pot rs
Sun 5	Ham	Ham	Ham	Chicken	Ham	Ham	Ham	Ham	Ham
Mon 6	Rst beef	Bf steak	Rst beef	Liver & bacon	Rst beef	Vl rst	Bf steak	Vl rst	Vl rst
Tue 7	Rst pork	Rst pork	Rst pork	Rst pork	Bf steak	Bf steak	Pk chops	Chicken	Chicken
Wed 8	Bf loaf	Liver & bacon	Bf loaf	Bf loaf	Chicken	Liver & bacon	Bf loaf	Bf loaf	Bf loaf
Th. 9	Liver & bacon	Bf steak	Chicken	Bf steak	Rst beef	Rst pork	Rst beef	Rstpork	rt pork

Schedule continued for 21 days.

Any two units served at the same time can be interchanged for following 21 days. As East and West, Nurses and Staff, Men and Women.

Chicken served for supper to one unit each week.

FIG. 1

to be served. The first step in the work is to plan the meats for 21 dinners Chicken is served to some group every day except Mondays and Fridays. Mondays are omitted because it is impossible to prepare chicken on Sunday and still allow employees extra time off, and Fridays are omitted because the Catholic patients object to having such a desirable meat on that day. The rest of the meat menu is planned throughout the house in the same manner, being sure not to have one group receive the same meat on the same day in two successive weeks. The potatoes are next planned in the same manner, avoiding such combinations as scalloped potatoes with gravy, or plain boiled

potatoes with a meat without gravy, such as a veal cutlet. Vegetables, relishes, desserts, and bakery stuff are then planned. All the many factors which go to make a good meal, such as color, flavor, dryness, etc., are to be considered when preparing the menu.

The initial labor in blocking out a menu according to this plan is enormous, but the after-work on each group or group of weeks is reduced

	DINNER	PATIENTS					EMPLOYEES							
1	Wed. April 6	Et	Wt	Ad	P	SP	S	N	W	M	NN	CB	CC	Order
Soup	Tomato broth Beef broth	*	*	*	*	* *	*	*	*	*	*			bowls
Meats	Roast lamb	*		*	*									92#
	Pot roast								*	*		50		55#
	Chicken		*											85#
Fry	Beef steak					*	*							55#
	Liver & bacon							*			*			liver 20# bacon 10#
Relish	Mint jelly	*		*	*									6 bu
	Pickles sweet		*						*	*				1 gal
	Jelly, apple					*	*				*	60		3 gal
Potato	Roasted	*												400#
	Mashed		*	*	*	*	*	*			*	60		
	Fried								*	*				
Vegetable	Peas		*	*	*	*	*	*	*	*	*	60		52#10
	Carrots as garnish	*	*	*	*	*	*				*			150#
	Cauliflower	*												
Dessert	Ice cream	*	*	*	*	*								
	Pie, peache						*	*	*	*				15#10
	Peach tapioca											60		

FIG. 2

greatly. The menu, when once planned, can be used rather indefinitely, since at the end of the first 21 days the hospital and house units can be shifted. As there are four units in the hospital's side, in addition to special diets which are in a class by themselves, and four units on the house side, this menu could be used practically for four periods of 21 days

each without repetition, as far as the units are concerned, and then the original menu can be repeated. Thus each unit has a new menu, with no work on the part of the dietitian except the substitution of new and unusual dishes and the seasonal delicacies. Such a plan allows time to study all new dishes with reference to cost, the available equipment, the labor required to prepare and serve that "certain dish," and its adaptability to the group to be served.

The menus are then tabulated on forms which divide the work of the different cooks as shown in figure 2. These forms are used in the office, the kitchen, and the bakery. From these, daily menus are made for each dining room and each floor in the sanatorium (figure 3). These daily menus include instructions for serving and the dishes needed. One

Date **April 6** Location **East** Food Report on Reverse Side

Breakfast	Use	Dinner	Use	Supper	Use
Baked apple	r	Tomato soup	c	Broth	c
Oatmeal	c	Cracker		Cracker	
Toast		Roast lamb	lp	Meat loaf	lp
Bacon	b&b	Mint jelly	pc	Spaghetti	lp
Coffee		Pot. roasted	lp	Fruit salad	ov
Cream	cr	Cauliflower	ov	Tea	
		Carrots (garnish)	lp		
		Ice cream	r		

Instructions: **Serve only one piece of carrot on large plate as a garnish.**

lp. large plate
b&b b & b plate
ov. oval
r. round
c. cereal
pc. paper chip creamer

FIG. 3

nurse on each floor is designated as the diet nurse and is responsible for the contact between the patient and the dietitian and for the service of food. She makes a written report on the back of each daily menu as to whether the food and service are acceptable or not, and why (figure 4). These reports are filled out before the trays are scraped and are returned to the dietitian, which gives her a truer index of what is eaten than does the weighing of garbage.

Clean, attractive trays and hot foods are essential. Our equipment for serving trays to bed patients is shown in figure 5. The trays are set up in the serving room in each wing, and then sent to the floors on tray-racks covered with canvas, which can be removed and washed. The food-carts are electrically heated, and carry food directly from the

kitchen to the floors. As the food is dished up at the bedside rather than in the kitchen, it is easy to give the patients a choice of meats and vegetables.

FOOD CONSUMPTION REPORT

Breakfast	Dinner	Supper
O.K.	Sent back for 4 servings of cauliflower. Patients like it very much. Would like vegetable creamed occasionally.	O.K.
Signed Susan Brown	Signed Susan Brown	Signed Susan Brown

FIG. 4

FIG. 5

The personal ideas of each individual about what constitutes the proper food for himself may interfere with the consumption of the food on his tray. Many times merely the presence of a certain dish which the patient does not like will be enough to prejudice him against the

entire tray. We attempt to overcome this by urging him to drink his milk and to eat the bread and butter on his tray, as that will give him approximately one-half of the desired number of calories per day and will be enough to sustain life and possibly prevent loss of weight. We then encourage him to eat at least one additional dish each day, until eventually he has been taught to eat his entire meal, which is planned for his bodily requirements and mode of living and not for his individual likes or dislikes.

Pirquet reported that in the postwar period in Austria food was scarce. In order to secure the proper amount of nutrition everything was used and there was practically no garbage, yet the children in his hospital in Vienna did well on this diet. Certain children were taken to Switzerland and Holland, where food was not so scarce. Upon their return to Vienna they were dissatisfied with the plain fare and would not eat it until they became hungry, even to the point of losing practically all they had gained in Switzerland and Holland. Yet the plain diet itself was ample, as was proved by the other children, who thrived on this diet in the hospital and who were able to continue to thrive on it in their homes in Austria after they had left the hospital.

Whenever possible the requests of patients for certain foods should be complied with, because even with the most careful thought and planning they do become "fed up" on sanatorium food, and satisfying a definite craving may entirely change their mental attitude. We have often found, however, that, when we serve the food which one group asks for, another group will be displeased. This, more than anything else, helps to dispel the idea that any one diet is necessary for the cure of their tuberculosis and to teach them that unless there is definite disease in the gastrointestinal tract any well-balanced, regulated diet is suitable for the treatment of their disease.

The plan outlined above is prepared for a large tuberculosis institution, but it may easily be adapted to a smaller hospital. If the sanatorium is small and every one has the same menu, the nine units will be replaced by one, but the menu could still be prepared in time-units of three or four weeks each and could be safely repeated at the end of three weeks, as no patient will remember what he had on Monday if he had the same thing on Monday three or four weeks later. Also, the diet can be varied according to seasons and to suit the market conditions as well in a small institution as in a large one. The value of written reports to the dietitian

is as great in small institutions as in a 700-bed sanatorium. Any plan that relieves the dietitian of unnecessary routine and gives her more time to plan out the larger things will be acceptable in the small institutions as well as in the larger one.

It is hoped that after a course of treatment in the sanatorium the patients will be able to leave the hospital so educated in the manner of proper eating that they will get the proper nutrition out of the money spent for the food used in their homes.

The food problem in a sanatorium is not new. It is due to the personal prejudice of each patient. It can only be solved through sympathy on the part of a dietitian for these individual prejudices and through the spirit of coöperation and give-and-take which prevails throughout the entire sanatorium. Nothing does more to gain the confidence and support of the patient than the feeling that he is an individual and that in so far as possible his opinion will be considered. With this spirit as a foundation and with the proper equipment, much can be done toward solving one of the most perplexing problems of sanatorium existence.

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TUBERCULOUS INFECTION OF THE LUNG IN EARLY INFANCY

A Report of a Case Observed from Twelve Weeks to over Five Years of Age[1]

JEROME L. KOHN

This case is presented for the following reasons: first, symptoms appeared when the child was nine weeks old, dyspnoea being present from the onset; second, the child had a positive Pirquet reaction when it was twelve weeks old; finally, the opportunity was given us to follow the case for a period of over five years, and the child is at present well.

CASE REPORT

A girl, aged twelve weeks, was admitted to the children's ward of the Mt. Sinai Hospital, August 30, 1922, with the complaint of difficulty in breathing for three weeks. The parents and one sister, five years old, were well. There was no history of tuberculosis in the family. The infant had been full-term, and delivery normal, the birth-weight being 6 pounds (2,880 gm.). It was entirely breast-fed, except for an occasional diluted milk mixture (during the last week before admission). At ten weeks it weighed 11 pounds (5,280 gm.). Three weeks before admission it developed noisy breathing, which the physician attributed to bronchitis. There was no cough or fever. Fourteen days later the patient experienced real difficulty in breathing. During this interval the baby had crying spells during which it had air-hunger, the face becoming engorged with blood. There was no cyanosis. These attacks were the same during the day and the night, and were becoming more frequent. The child had been given a therapeutic dose of roentgen-ray irradiation twenty-four hours before admission.

Examination

Physical examination showed a well-developed, well-nourished infant, acutely ill, and breathing with great difficulty but not rapidly. There was stridor, and retraction of the suprasternal fossa on inspiration. The patient was not cyanotic. The head, eyes, ears and throat were normal. The right side of the chest was fuller, and there was slight dulness and diminished breathing over

[1] From the Department of Pediatrics, Mount Sinai Hospital, New York City.

the right upper lobe, anteriorly and posteriorly. There was also diminished breathing over the right lower lobe. The left lung was normal. The heart, abdomen, extremities and skin were normal. Tuberculides were not present, nor were lymph nodes palpable.

The leucocytes were 7,700 per cmm., polymorphonuclears 66 per cent, lymphocytes 29 per cent and monocytes 4 per cent. The Pirquet test was positive. The blood Wassermann was negative. A roentgenograph showed atelectasis of the right upper lobe, with emphysema of the lower portion of the right lung, and displacement of the heart and mediastinum to the left. Roentgenoscopic examination gave no additional information. On admission the child's temperature was 103°F., but the temperature after the first day in the hospital was normal.

Course

On September 1 the child's general condition was about the same. When taking the breast or the bottle it would stop after taking an ounce. Its cry was hoarse, the suprasternal retraction was unchanged, and the entire anterior portion of the right chest, including the sternum, was dull to percussion. In both axillae resonance was normal, though slightly lower-pitched over the left side. Breathing over the right apex anteriorly was louder than over the left apex, but it was normal in character. The left border of the heart was pushed over, and the precordial dulness obliterated almost to the left clavicular line. The apex beat was not palpable and was best heard outside the nipple line. Posteriorly there was slightly diminished resonance over the right scapula, both bases being normal.

On September 3 the child's dyspnoea was increased, there was an expiratory and inspiratory wheeze, the respirations were 72 per minute, and the chest signs were unchanged. Under anaesthesia a bronchoscope with a 6-mm. tube was passed. The mucosa at the lower end of the trachea was loose and redundant, the tracheal spur was thickened, particularly anteriorly, and the calibre of the right main bronchus was narrowed to a crescentic slit. The calibre of the left bronchus was perhaps slightly narrowed. There was evidently pressure from without on the right main bronchus, due to involvement of structures in the mediastinum.

Soon after the bronchoscopy the child began to breathe more easily, and a roentgenograph taken on September 7 showed less atelectasis of the right upper lobe and less emphysema of the right lower lobe. The child continued to improve and gained weight, and on September 13 the lung signs were almost normal. From September 8 to September 19 the child received ultraviolet irradiations, gradually increasing until it was receiving five minutes anteriorly and posteriorly. It was discharged September 19, 1922, breathing normally

and weighing 11 pounds, 1 ounce (5, 310 gm.). The leucocyte count just before discharge showed polymorphonuclear cells 64 per cent, lymphocytes 35 per cent, and monocytes 1 per cent.

Second Admission

The child returned to the hospital three weeks later. Since discharge it had gained one pound (480 gm.), and had remained well until three days before admission, when the dyspnoea returned. It had received roentgen-ray therapy on the day before, as well as on the day of this admission. On examination it was very dyspnoeic, with suprasternal retraction. The respirations were 60 per minute. The right upper lobe was dull, and there was harsh breathing. The remainder of the lung was hyperresonant, but there was dulness over the sternum. A roentgenograph showed complete atelectasis of the right upper lobe and emphysema of the right lower lobe. The heart and mediastinum were again displaced to the left.

On October 14 the child was a little better, but stridor and retraction were present. On October 17 it was worse, the cough had a metallic sound, and the child was slightly cyanotic and had an anxious look. There were dulness and diminished breathing over the entire right lung; also diminution of breath-sounds. On October 19 the child was better, and more air was coming through into the right lower lobe. A roentgenograph on October 23 showed partial aeration of the right upper lobe, with a decrease of the bronchostenosis of the lower-lobe bronchus, the displacement of the mediastinum being slight. Until October 31 the respirations were from 50 to 60 a minute; thereafter about 30 a minute. On November 6 the child's condition was good; it was gaining in weight and stridor was present, but it was dyspnoeic only after taking the breast or bottle. A roentgenograph on November 6 showed moderate atelectasis of the right upper lobe, but the emphysema was gone. At the root of the right lung there were a number of dense shadows, which were probably due to tuberculous lymph nodes. Except for a mild upper-respiratory infection the child continued to improve, and was sent home December 5, 1922, weighing 14 pounds (6,720 gm.). It was breathing normally, and physical examination showed only high-pitched respiration over the right upper lobe.

For the last five years this child has been seen regularly. It has progressed normally. It has had very few upper respiratory infections, and has increased in weight and length normally. It has had Pirquet tests about twice a year, of which the reactions have always been moderately positive, with very little change in their intensity. The last Pirquet test, made in the autumn of 1927, was positive. In February, 1928, the child had pertussis, from which it recovered completely and without any apparent effect on its tuberculosis. The serial roentgenographs will be discussed in the paper.

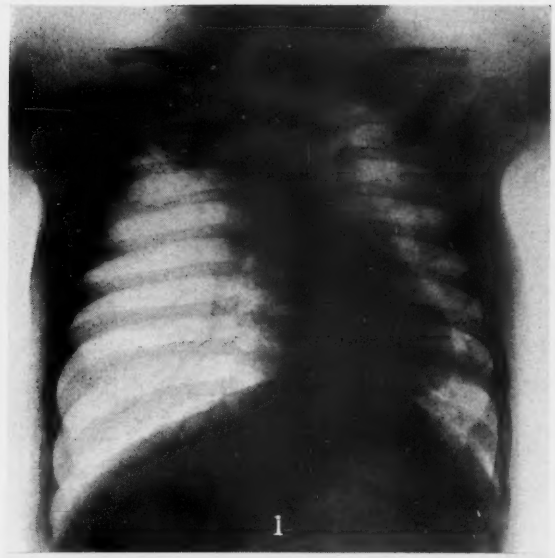
COMMENT

I shall not discuss the development of a primary tuberculous infection in this report, as that subject has been gone over fully very recently by Stoloff (1). In the case here reported there was no positive history of direct exposure, the members of the immediate family all being clinically well. The child had been entirely breast-fed and, as noted in the history, symptoms first appeared when it was nine weeks old. It was born at home, and the only person suspected as the source of infection was a colored servant who came in part-time, about three times a week. She left when the child was about nine weeks old, and could not be found when looked for later.

The patient was sent to the hospital with a diagnosis of thymic obstruction or aspiration of a foreign body. In fact, bronchoscopic examination showed almost complete bronchostenosis, and a roentgenograph (figure 1) showed atelectasis of the right upper lobe, undoubtedly due to compression on the eparterial bronchus by an enlarged tuberculous lymph node or nodes; there was also emphysema of the lower lobe, due to partial stenosis of the lower bronchus. Perhaps this emphysema was compensatory. Because of the increased lung volume there was displacement of the mediastinum and heart to the left and depression of the right side of the diaphragm.

A roentgenograph, taken eight days after admission, showed partial aeration of the right upper lobe, with decrease in volume of the right lower lobe. The child was breathing much more easily. Before admission the child had received two treatments of deep roentgen-ray irradiation, but none after admission. While in the hospital and after discharge it received ultraviolet irradiations.

On the second admission a roentgenograph again showed atelectasis of the right upper lobe and emphysema of the lower lobe, with displacement of the heart and mediastinum to the left. On this admission the patient again received two treatments of deep roentgen-ray irradiation. The dyspnoea was less soon afterward, and a roentgenograph (figure 2), taken two weeks later, showed only moderate atelectasis and slight displacement of the mediastinum. A roentgenograph (figure 3), taken four weeks after the second admission and less than three months after the onset of symptoms, showed for the first time a dense shadow at the root of the right lung, probably due to enlarged, diseased lymph nodes. A roentgenograph (figure 4), taken five and a half months after



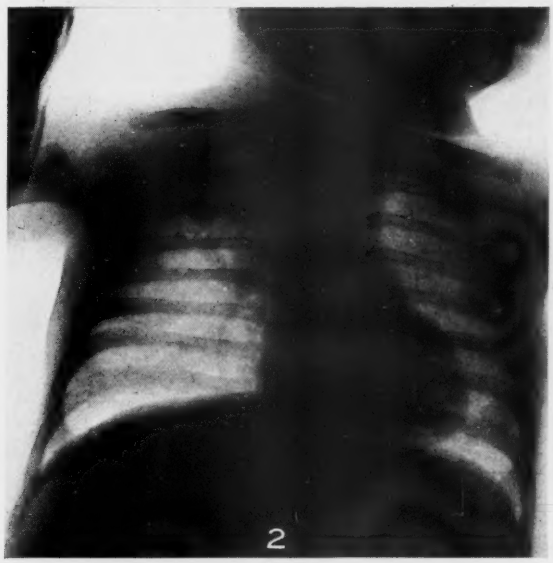
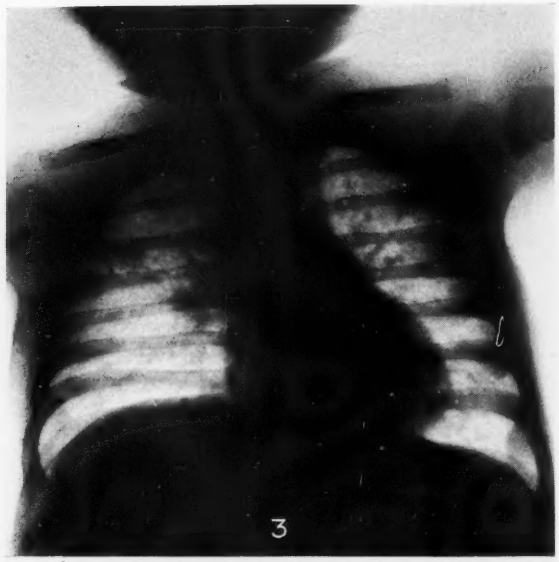


FIG. 1. September 1, 1922. Patient aged twelve weeks. Was having inspiratory and expiratory dyspnoea. Roentgenograph shows complete atelectatic collapse of right upper lobe, emphysema of right lower lobe with increase of volume, displacement of heart and mediastinum to left, and depression of right diaphragm. This picture may be explained by compression of tuberculous lymph nodes on the bronchi, causing complete stenosis of the eparterial bronchus and partial stenosis of the lower bronchus.

FIG. 2. October 23, 1922. Patient aged nineteen and one-half weeks. Improving, dyspnoea much less, and more air coming through into the right lower lobe. Roentgenograph shows partial aeration of right upper lobe, with decrease of signs of bronchostenosis of the lower-lobe bronchus, the displacement of the mediastinum being slight.



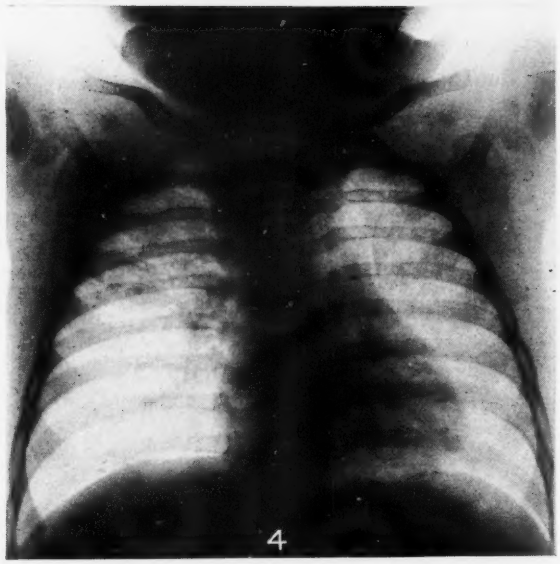
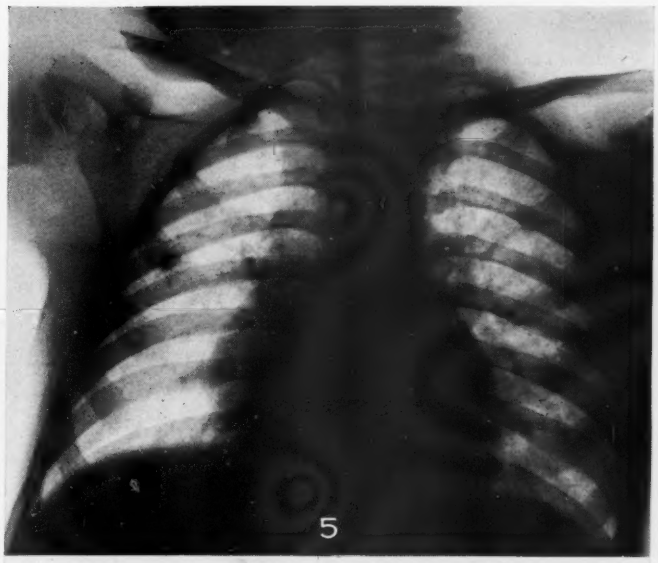


FIG. 3. November 6, 1922. Patient aged twenty-one and one-half weeks, thirteen weeks after onset of symptoms. Condition good; stridor present but dyspnoea only after taking breast or bottle. Roentgenograph shows further aeration of right upper lobe, disappearance of lower-lobe bronchostenosis, and for the first time there is adenopathy at the right hilum.

FIG. 4. January 23, 1923. Patient aged seven and one-half months, five and one-half months after onset of symptoms. In good physical condition. No dyspnoea or stridor. Roentgenograph same as in figure 3, except that for the first time there are indistinct signs of pulmonary infiltration in lower part of right upper lobe.



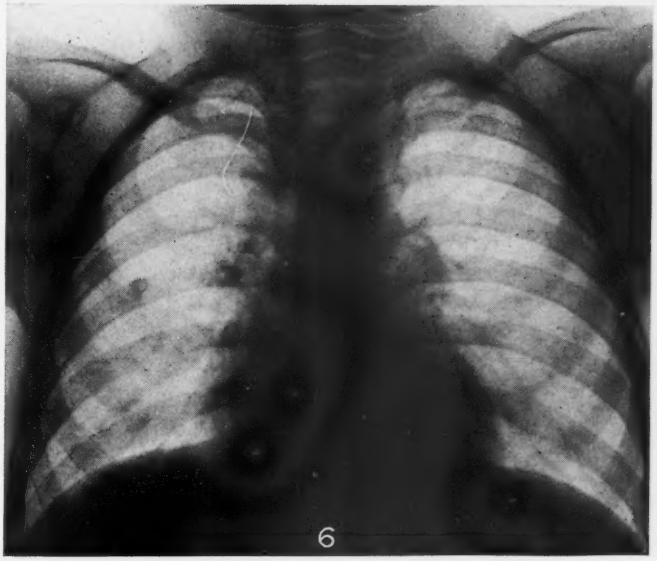


FIG. 5. August 28, 1925. Patient aged three years, two months. In good condition. Roentgenograph shows calcified area, the size of a pea, on lower portion of right upper lobe, undoubtedly the primary lesion. There is also distinct caseation in right bronchial lymph nodes.

FIG. 6. May 20, 1927. Patient aged five years. In good condition. The primary lesion is calcified and more compact than that in figure 5, and the lymph nodes at the right hilum give a denser shadow.

onset, showed for the first time signs of pulmonary infiltration in the right upper lobe. However, one could not definitely state from the appearance of the infiltration that it was tuberculous in nature. This area was probably the primary site of infection.

A roentgenograph (figure 5), taken three years after onset, showed evidence of healing, with a calcified primary lesion, the size of a pea, at the site of the previous pneumonic infiltration and also caseation of the lymph nodes at the right hilum.

A roentgenograph (figure 6), taken five years after onset, showed the primary lesion to be still more compact, and the lymph nodes gave a denser shadow.

DISCUSSION

From a clinical view point this case is interesting, in that one sees a tuberculous infection so early in infancy. The fact that the Pirquet test was positive before the child was twelve weeks old, would lead to the conclusion that the infection was implanted at least three or four weeks before. It takes from three to four weeks from the onset of the infection for the tuberculin reaction to become positive. The clinical signs in this patient were first noted when it was nine weeks old, and, as it usually takes at least three weeks from the onset of an infecton to first clinical manifestations of illness, we can safely say that this child was infected no later than when six weeks old. The source of the infection was most likely the colored woman who worked in the house.

It is unusual to be able to diagnose the primary complex so soon, as there are so very few symptoms in the beginning of the disease. The primary lesion is too small to give any signs. Because of the compression of the tuberculous lymph nodes on the bronchus symptoms appeared earlier in this case. We know that enlarged lymph nodes, so located, often give expiratory difficulties. Schick (2) and Sluka (3) reported a number of such cases in early infancy. In the case here reported there was both inspiratory and expiratory difficulty, perhaps because of the fact that in so young a child the lumina of the bronchi are very narrow. That the primary focus was small can be judged from the roentgenographs taken three years and five years later. These plates also bring out strikingly the well-known fact that, although the primary lesion is small, the lymph-node enlargement may be very extensive, and seemingly out of all proportion to the primary focus.

The tuberculous infection in this infant caused very little febrile disturbance, for only on the day of admission was the temperature over 100°F. Without the positive tuberculin reaction one could not have made a diagnosis so early. This shows the value of the use of the tuberculin test, for without it the case would probably have been diagnosed as an enlarged thymus causing compression. Of course such thymic enlargement could not be ruled out absolutely.

Clinically one could not differentiate, from the physical signs alone, whether the infiltration at the apex was due to pneumonia or to atelectasis from mechanical pressure. However, the rapid clearing of the upper lobe signified a mechanical process.

The fact that while under observation the child had so little febrile reaction, and gained normally, would lead one to believe that the exposure to tuberculous infection was short, not often repeated and not massive.

In regard to treatment, it is difficult to evaluate the effect of the roentgen-ray irradiation. There was no definite improvement after the first treatment, but there seemed to be some after the second.

SUMMARY

1. A case is presented of tuberculosis in an infant twelve weeks old, and probably infected six weeks before. The Pirquet reaction was positive at twelve weeks, and first symptoms appeared at nine weeks of age.

2. The clinical picture simulated a case of foreign-body obstruction or thymic compression.

3. One could by means of serial roentgenographs note the development and recession of the disease.

4. The primary focus (Ghon) was first observed on a roentgenograph taken when the child was three years and two months old.

5. The source of the infection was never definitely ascertained.

6. The prognosis of tuberculosis even in early infancy is not necessarily fatal. This child developed normally, and is in excellent health over five years after it first came under observation.

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INTRATHORACIC TUBERCULOUS LYMPHOMA[1]

H. WESSLER

The cases of intrathoracic lymphoma here reported represent a very unusual form of tuberculosis of the lymph node. Aside from their clinical interest as a type of tuberculosis not previously described, they have an important bearing on the pathogenesis of this disease as it occurs in adults. Furthermore, in some respects they bear a suggestive resemblance to Hodgkin's disease, whose identity with lymph-node tuberculosis is maintained by an increasing number of pathologists in recent years.

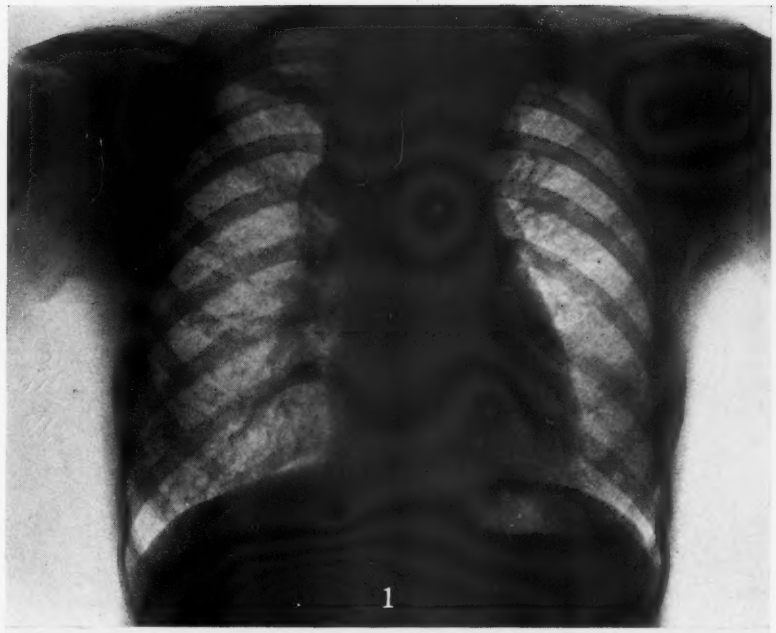
The clinical histories of these cases are briefly as follows:

Case 1: C. C. Age, 20 years. June, 1926. No previous illness. Two months ago became ill with fever at night, headache and an upset stomach. Since then coughed much at night. Lost 20 pounds in last two months. Feels tired in afternoon. *P. E.:* Undersized, poorly nourished girl. No enlarged lymph nodes. *Chest:* Dull over left apex, with harsh breathing. Pulse 104; temperature 100°; Hb. 48 per cent. *Roentgen Examination:* Marked enlargement of upper tracheobronchial lymph nodes on both sides; a tuberculous process undergoing fibrosis at left apex (figure 1). This patient was under observation for one year with little change in her condition. The bronchial lymph nodes remained unchanged in size. There was evidence of increasing fibrosis of the tuberculosis at the left apex.

Case 2: M. D. Age, 19 years. March, 1926. No previous history of tuberculosis. In last three years lost 30 pounds. No cough or fever. Patient came under observation for renal colic; passed small calculus. During stay in hospital had slight elevation of temperature. *P. E.:* Poorly nourished girl, with no evidence of pulmonary disease. No enlargement of superficial lymph nodes. *Roentgen examination* showed marked enlargement of right paratracheal nodes and a massive enlargement of lower tracheobronchial nodes (figure 2). This patient was under observation for six months, with no change in her condition.

Case 3: M. C. Age, 15 years. May, 1925. Had measles five years ago. Five months ago began to have dyspnoea on climbing stairs. Became in-

[1] From the medical service of Mount Sinai Hospital, New York City.



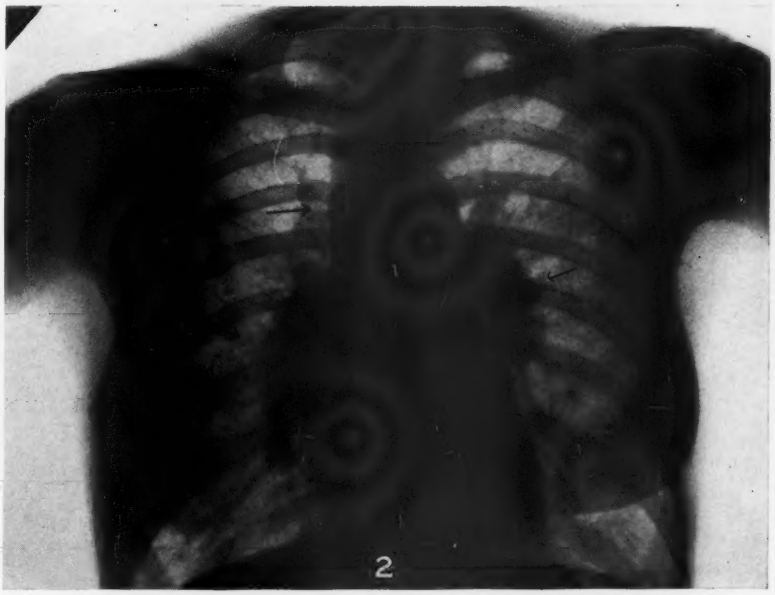
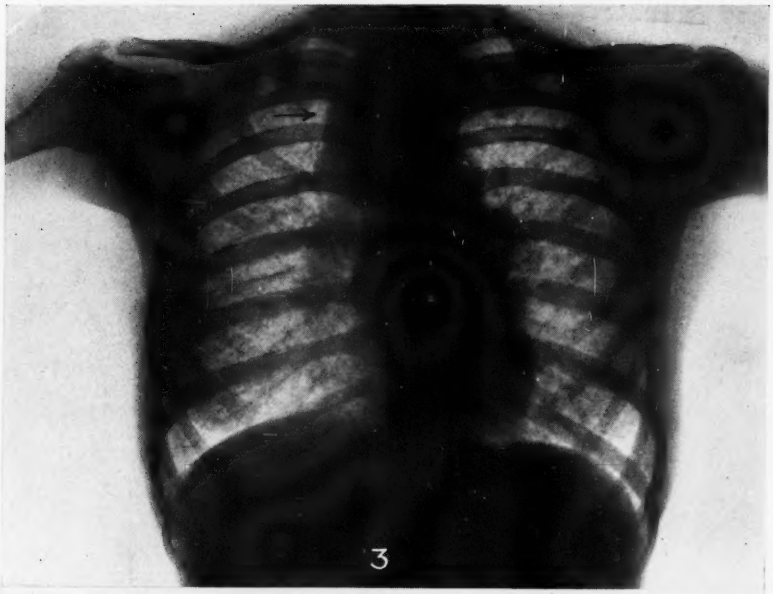


FIG. 1. Case 1. Large lymphomatous masses in superior mediastinum. Tuberculous process at left apex.

FIG. 2. Case 2. Enlargement of right paratracheal lymph nodes indicated by arrow. Lymphomatous enlargement of bronchial lymph nodes on both sides.



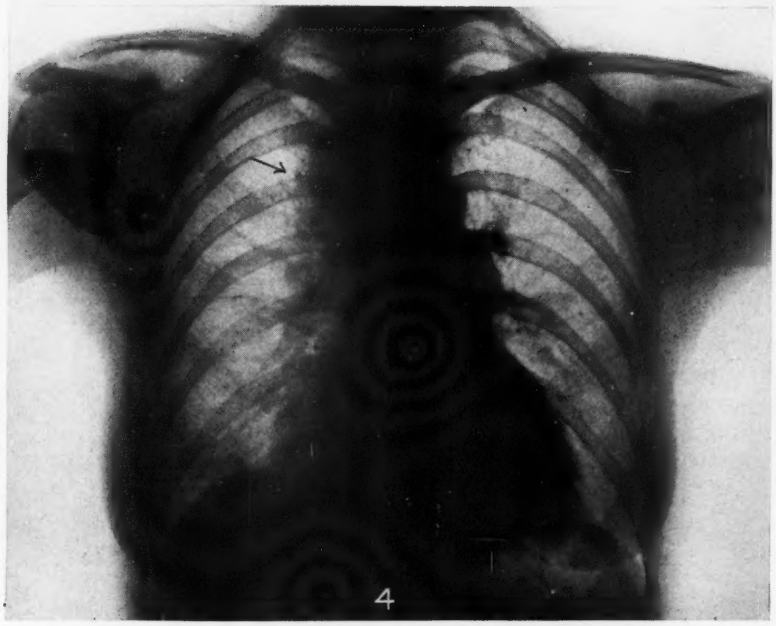


FIG. 3. Case 3. Extreme enlargement of right paratracheal group of lymph nodes indicated by arrow. Moderate enlargement of bronchial lymph nodes. Miliary tuberculosis of lungs.
FIG. 4. Case 4. Marked enlargement of right paratracheal lymph nodes.

creasingly weak, until three weeks ago when began to cough, with bloody sputum. The same day had slight nosebleed and fever. Since then has had four nosebleeds, followed by bloody sputum. Has had constant fever for two weeks, with profuse sweats at night. Three days ago got haemorrhagic rash over her legs, which has persisted. *P. E.:* Poorly nourished girl. Moderate number of petechiae on legs. Lungs show a few fine râles below angle of scapula. Dilated bleeding vessels on either side of nasal septum. Few small cervical lymph nodes. Hb. 90 per cent; red cells 4,700,000; leucocytes 6,200; platelets 2,000; coagulation time 12 minutes; bleeding time 17 minutes; tourniquet test positive,—no clot retraction in 48 hours. *Diagnosis:* Thrombocytopoenic purpura haemorrhagica. Spleen slightly enlarged. Was under observation until July 6, during which time temperature of 100° to 101° daily and at various times moist râles in various portions of lungs. Excised cervical lymph node showed fibrosis with foci of caseous miliary tubercles microscopically. *Roentgen Examination:* Massive enlargement of paratracheal lymph nodes on the right side, forming mass the size of a lemon. Lower group of tracheobronchial nodes also much enlarged on both sides. Lungs studded with innumerable miliary tubercles. Roentgen appearance of lymph nodes identical with that often seen in Hodgkin's disease (figure 3).

Case 4: F. M. Age, 25 years. May, 1926. No previous personal or family history of tuberculosis. Three years ago said to have had pleurisy on right side. Has had number of attacks of grippe since 1918 epidemic. In last four months has had slight menstrual irregularities. For the last four months, following attack of grippe, has had joint pains and swellings. Has lost 14 pounds and grown weak. During this time cough, off and on, with slight expectoration. Some pain in chest. Has had a large swelling on left side of neck which has disappeared spontaneously. *P. E.:* Very pale. Appearance of chronic illness. Slight tenderness of small joints of hand without swelling. Small lymph node behind left sternomastoid muscle; also few small lymph nodes in supraclavicular fossa on both sides. Hb. 52 per cent; red cells 4,000,000; leucocytes 13,600; polymorphonuclears 79, lymphocytes 16, mononuclears 5. Sputum negative for tubercle bacilli. No abnormal physical signs in chest. *Roentgen Examination:* Large mass in upper mediastinum on right side, presumably due to mass of tuberculous paratracheal lymph nodes. Lower group of nodes not much enlarged (figure 4). Lymph node removed from the neck showed evidence of tuberculosis. During stay in the hospital of five weeks there was slight fever rising occasionally to 101°. Patient has been observed now for one and a half years; has remained well and developed no other lymph-node enlargement.

Case 5: M. E. Age, 22 years. September, 1920. Dry pleurisy ten years ago. No other illness since. Present illness began six months ago with dull pain in supraclavicular region continuing three months. Since then has felt tired and weak, and has had slight elevation of temperature and lost 35 pounds. Has morning cough, with small amount of sputum. Has felt enlarged lymph nodes on right side of neck for four months which have become larger and more numerous in last two months. *P. E.:* Fairly well-nourished man. Some dulness at right base and diminished breathing in both supraclavicular regions.

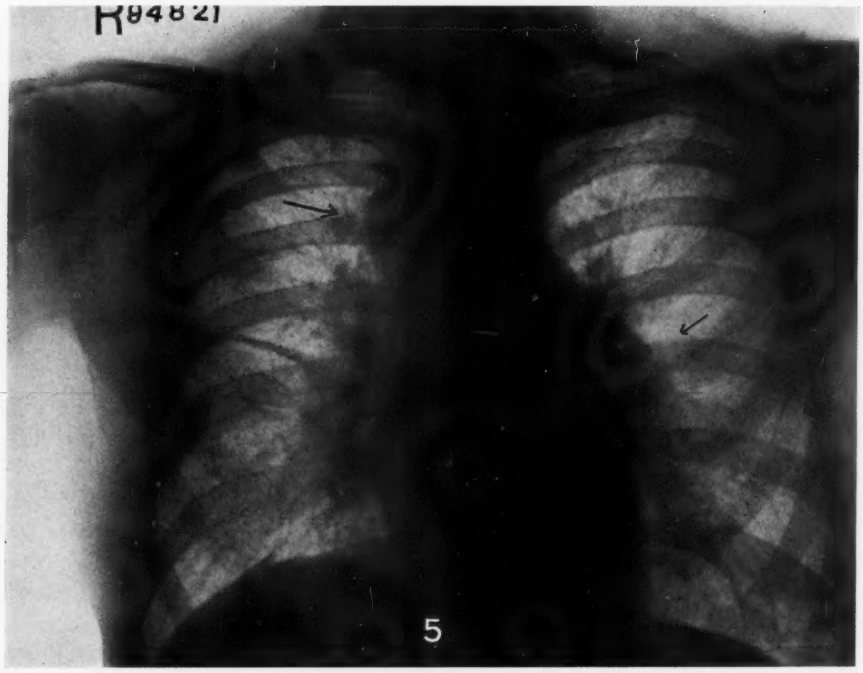


FIG. 5. Case 5. Massive enlargement of right paratracheal lymph nodes. Large lymphomatous masses involving bronchial and bronchopulmonary lymph nodes on each side. Thickening of right interlobar fissure.

Large lymph nodes, size of almond, discrete, firm and not tender above clavicle. Spleen felt 5 cm. below rib-border. Hb. 110 per cent; red cells 6,000,000; leucocytes 9,200; polymorphonuclears 69, lymphocytes 27, eosinophiles 2 per cent. No fever. Excised lymph node showed miliary tuberculosis. During stay in hospital of five weeks some loss of weight. Clinical impression, aside from examination of lymph node, that of Hodgkin's disease. *Roentgen Examination:* Marked enlargement of all intrathoracic lymph nodes. Right paratracheal nodes form oval mass, size of lemon. Lower tracheobronchial nodes

also form large lymphomatous masses extending far out into lung fields. Right interlobar fissure much thickened, and may represent reaction to recent primary lesion in lung (figure 5).

COMMENT

We may summarize the clinical features of these cases as follows:

The patients were all young adults and, with one exception, were females. They were the subjects of a tuberculous infection which manifested itself in the usual way by fever of moderate degree, weakness and loss of weight. In addition there were such less common evidences of toxaemia as purpura haemorrhagica and rheumatic pains.

The major signs of the disease consisted in an enlargement of the mediastinal lymph nodes, which in some of the cases was of massive proportions. That these changes were of recent origin is to be inferred from the duration of the symptoms, which in four of the cases had lasted only from two to six months and in only one case was the duration presumably longer, that is, three years. This is moreover rendered likely by the discovery of miliary tubercles in the excised lymph nodes of two of the cases. Some of the patients were apparently in the active stage of the disease, whereas in others the symptoms had subsided.

The lymph-node enlargement presents two unusual features: first the practically exclusive involvement of the intrathoracic nodes and, second, their extreme hyperplasia, which justifies our description of them as lymphomata. Aside from such diseases as leukaemia, lymphosarcoma and particularly Hodgkin's disease, such an enlargement of the lymph nodes in the chest of adults does not occur. It is clear that we have here a different type of tuberculous infection of the lymph nodes from that ordinarily found in adults. This difference will be apparent if we revert for a moment to tuberculosis of the lymph nodes as it is found in infants.

Tuberculosis of the bronchial lymph nodes in infants manifests itself by massive enlargements and extensive caseation. We regard these as the reaction to a primary focus in the lung, which appears to be determined by the wide lymphatic channels of the infant and by an innate reactivity of the lymph nodes which has not been modified by any previous tuberculous infection. Should the infant survive the infection, the lymph nodes undergo gradual induration and calcification, and become smaller; for this and probably other reasons they are no longer capable of such an extreme enlargement when they are reëxposed to infection in later childhood or adult life. In short, the bronchial nodes of adult

tuberculosis are small, indurated and anthracotic, and they present the familiar small dense shadows at the root of the lungs which are commonly seen on the roentgen films. It is needless to say that this latter type of lymph-node tuberculosis produces no symptoms and has no clinical importance.

If we apply these considerations to the five cases I have here described it is evident that we are dealing with a type of lymph-node disease which is characteristic of infantile tuberculosis, whose advent in these patients, however, has been delayed until early adult life. The roentgen appearance of these nodes reproduces in every detail that which is often seen in the massive tuberculosis of the lymph nodes in infants.

A further analogy to the lymph-node disease of infants is seen in the marked enlargement of the paratracheal group of nodes which occurred in every case. These nodes are practically never enlarged in the tuberculosis of adults but are frequently seen in the same disease in infants. They are variously described as the upper tracheobronchial or paratracheal lymph nodes, and form a mass sometimes of considerable size which lies adjacent to the trachea and between it and the upper-lobe bronchus. They have been thoroughly described by Rach in tuberculous infants (1).

How shall we explain such an atypical response of the lymphatic apparatus as is exhibited by these cases? In view of the similarity to infantile tuberculosis must we not assume that in these patients we are witnessing a primary tuberculous infection and that the marked enlargement of the lymph nodes represents the response of lymph nodes previously unaffected by the tubercle bacillus?

In our search for the primary lesion we must be guided by the principles of tuberculous infection which underlie the same disease in childhood. If we adhere to the well-established postulates of Parrot (2), which have been amply confirmed by Küss (3) and Albrecht (4) among others, we cannot consider these cases as primary tuberculosis of the lymph nodes but must rather view the lymph-node enlargement in relation to some pulmonary focus which is tributary to the nodes. Unfortunately, neither the clinical examination nor the roentgen film revealed any primary lesion of the lung except in one case. However, this is not a valid argument against its existence, as it is well known that the primary lesion may be so small as to escape clinical detection and that within a short time it may almost or completely disappear, leaving behind it a disproportionate lymph-node enlargement. The miliary tuberculosis of the lungs in case 3 can only be regarded as a secondary

tuberculous manifestation, which succeeded the adenopathy and which was probably the result of a bacillosis.

In short, if we proceed in our speculations in accord with accepted principles as to the pathogenesis of tuberculosis, it is plausible to conceive that these five young adults were previously unaffected by tuberculosis and that recently they contracted the disease presumably as a primary focus in the lung. Following this and associated with the usual symptoms of toxaemia, they acquired a tuberculous adenopathy of the regional nodes of the infantile type. In several of the cases, in addition, there was evidently a bacillosis, with a dissemination of the disease, as shown by miliary foci in a cervical node and in one case by a miliary tuberculosis of the lungs.

In conclusion, the relation of these cases to tuberculosis of the lymph nodes in general may engage our attention, especially to those forms of generalized tuberculosis of the lymph nodes which have given rise to much confusion, both clinically and pathologically. The tuberculous nature of certain forms of extensive lymphatic disease was recognized by Delafield (5), who in 1887 reported a universal lymphadenopathy and by Askanazy (6), who described a distinctive form of lymph-node tuberculosis. Clinically, these cases have occasionally been confused with pseudoleukaemia and Hodgkin's disease, which they may so closely resemble that only microscopic examination of a lymph node will reveal their true nature. On the other hand, there are cases of this pseudoleukaemic form of tuberculosis in which only bacterial staining or animal inoculation will prove them tuberculous. The cases here described exhibit on the roentgen film the characteristics of a true lymphoma, and in this respect they resemble the pseudoleukaemic form of tuberculosis. However, they differ from the latter, and stand in a group by themselves, owing to the absence of any significant enlargement of the external lymph nodes from which their true nature may be determined. Except for the three cases in which small cervical lymph nodes were found to be tuberculous microscopically, they might all be regarded as lymphomata belonging to the group of pseudoleukaemia or Hodgkin's disease.

Baumgarten (7) in particular sees in the pseudoleukaemic form of tuberculosis a significant relationship to Hodgkin's disease, of which he regards it as a transitional form. This view is supported by the experiments of Weingarten (8) and Lichtenstein (9), who produced the microscopic appearance of Hodgkin's disease by the injection of tubercle bacilli or tuberculous lymph nodes into guinea pigs. The recent work of Fraen-

kel and Much (10) has again stimulated interest in this problem. These investigators have succeeded, by the injection of lymph-node material from cases of Hodgkin's disease in which Much granules were found, in producing typical tuberculosis in animals, and they accordingly regard Hodgkin's disease as a variety of tuberculosis of the lymph nodes.

It is not the purpose of this paper to make the observations here recorded serve as evidence of the identity of these two diseases. However, certain clinical and roentgenological resemblances are so striking that one cannot forbear to point them out. Wessler and Greene (11), in a study of the intrathoracic changes of Hodgkin's disease, called attention to the typical appearance of the lymphomatous masses seen in the chest. Most striking was the almost constant enlargement of the paratracheal lymph nodes, which assumed a size and configuration seen in practically no other disease. The similarity with the appearance found in the cases of tuberculous lymphoma here recorded is so striking that the diagnosis of Hodgkin's disease on this basis alone was rendered probable in most of the cases, were this not refuted by the other clinical features. In case 5, for example (figure 5), we have an instance of this form of the disease, in which the clinical signs, consisting of characteristic lymphomatous masses in the chest and an enlarged spleen, simulated to the smallest detail the picture of Hodgkin's disease. This diagnosis would have been maintained were it not controverted by the finding of tuberculosis in a small lymph node in the neck.

The subject of the relationship of Hodgkin's disease and tuberculosis of the lymph nodes is still very much in dispute. It is, therefore, proper to focus attention on this unusual form of lymph-node tuberculosis, which, at least in some of its clinical and roentgenological manifestations, evinces a marked similarity to Hodgkin's disease.

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TUBERCULOSIS OF THE ANTERIOR MEDIASTINAL LYMPH NODES

A Case Report with Postmortem Findings[1]

RICHARD C. BUCKLEY[2]

Tuberculosis involving the anterior mediastinal lymph nodes is uncommon. Among 115 cases of pulmonary tuberculosis the writer has observed the condition in two instances, both of which were unusual cases. In the first case one of the lymph nodes was attached to the parietal pericardium and had ruptured into the pericardial sac, and a tuberculous pericarditis resulted. The second case, which is here presented, simulated an aneurysm of the aorta or a mediastinal tumor. A similar case report was not observed in the literature.

CASE REPORT

Clinical History: The patient, a white male hospital worker, aged 65 years, was admitted to the United States Veterans Bureau Hospital No. 41 on May 27, 1924, with the complaints of "heart trouble, pains in the left chest, cough and expectoration." Weakness and a pulmonary haemorrhage had forced the patient to be hospitalized in 1913. From 1913 to 1917 the pulmonary condition was considered to be an active tuberculous one. In 1917 the patient was diagnosed as an arrested case and he returned to his former occupation for a period of seven months. Then he had a second pulmonary haemorrhage and the signs and symptoms of a pleurisy, and was again hospitalized. The patient was at several Government hospitals before admission to Hospital No. 41.

The physical examination on admission showed a pulse-rate ranging from 75 to 102 per minute, a temperature ranging from 36° to 37.1°C., and a blood-pressure of 140/76. There was no cyanosis. The physical signs of a far-advanced pulmonary tuberculosis, with cavitation in the left upper lobe and a diffuse bronchitis and pulmonary emphysema, were present. There was no observed increase in cardiac dulness. The X-ray plates showed, in addition to extensive pulmonary lesions, a large mediastinal shadow, which obscured

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the usual aorta shadow. Tubercle bacilli were demonstrated in the sputum. The Wassermann reaction was negative.

During the stay of 25 months in this hospital the patient had countless small haemorrhages, and the sputum was persistently streaked with blood. "Asthmatic attacks" were constant. They consisted of a relatively short

FIG. 1. TUBERCULOSIS OF MEDIASTINAL LYMPH NODES WITH COMPRESSION OF TRACHEA AND ARCH OF AORTA. CHRONIC ULCERATIVE PULMONARY TUBERCULOSIS

inspiration followed by a prolonged and difficult expiration. These attacks began in 1913, but were especially severe during the stay in this hospital. Transient attacks of cyanosis, dyspnoea, and oedema of the extremities made a diagnosis of arteriosclerotic heart disease with congestive failure seem certain. The clinical impression was that the respiratory difficulty was due to "cardiac asthma," but there was no explanation offered for the increase of shadow in the mediastinum, as seen in the X-ray plates. Death occurred on July 27, 1926.

Necropsy Report: The postmortem examination was made 22 hours after death. The appended anatomical diagnosis enumerates the gross findings. Of particular interest was the mass of tuberculous anterior mediastinal lymph nodes which were firmly encapsulated and which compressed the arch of the aorta and the trachea. The microscopic examination showed a necrotic tissue with a typical proliferative type of tuberculous reaction at the periphery. There was no evidence of calcification. The mass could be easily separated from the surrounding tissues. The attached drawing (figure 1) emphasizes the exact location and compression effects.

Anatomical Diagnosis: Primary: (a) Chronic ulcerative pulmonary tuberculosis; pleural adhesions; rupture of blood vessel in wall of tuberculous cavity with haemorrhage; tuberculosis of anterior mediastinal lymph nodes, with compression of arch of aorta and trachea; pulmonary emphysema; cardiac dilatation. (b) Generalized arteriosclerosis, with special involvement of the coronary arteries and arteries of the lower extremities; chronic passive congestion of the viscera.

Subsidiary: Adenoma of prostate; hypertrophy and dilatation of the bladder; decubitus ulcers; varicose veins.

TISSUE REACTION IN TUBERCULOSIS[1,2]

R. S. CUNNINGHAM

In deciding the scope of my discussion for to-day I have been influenced by two considerations: first, that it is quite impossible to cover more than a very small part of the field in the time at my disposal; and second that, since I must be limited in my subject matter, it is wisest to discuss that phase of the subject which seems to offer the most fruitful opportunities for future work, that is, the reactions of the tissues in tuberculosis or, in other words, tissue immunity.

Before approaching the subject proper, I wish to refer briefly to the activities of the Research Committee of the National Tuberculosis Association, since much of the work which will be mentioned below has been carried out as part of the general plans of this committee. Under the able direction of its chairman, Dr. William Charles White, this committee has inaugurated one of the most remarkable ventures in cooperative research that has ever been undertaken. The workers engaged in this series of studies comprise chemists, anatomists, pathologists and bacteriologists. They are accomplishing far more as a group than many times their number could if working independently. This result is due to both the industry and coöperative spirit of the individual workers and to the wise leadership of Dr. White.

In considering the present status of tuberculosis it is significant that we have made but little progress with regard to any specific medical treatment since the days of Laennec. Internal medication has proved of little avail. Chemotherapeutic agents of many kinds have been suggested and each of these in turn, after raising the hopes of many sufferers, has led but to new disappointments. This is well illustrated by the world-wide interest in sanocrysin, which is now generally, if not universally, believed to be of no positive value, if indeed it is not definitely harmful. Tuberculin is used for the treatment of selected cases, es-

[1]From the Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee.

[2]Read at a symposium presented before the joint meeting of the American Public Health Association and Section N of the American Association for the Advancement of Science at the Nashville Meeting, Nashville, Tennessee, December 28, 1927.

pecially in children, and undoubtedly does give beneficial results, but among the profession at large it has received but little support as a therapeutic measure of importance. Heliotherapy has likewise been found to be of use, but the question has often been raised, especially by those interested in sanatorial methods, as to the proportional benefit derived specifically from the treatment with light and the extent to which this improvement is in reality the result of the coincidental rest in bed and general regimen. Finally, vaccine therapy and serotherapy have been tried by innumerable investigators, and in almost every instance the results have been disappointing, if not wholly useless. So uniformly has this been true that it seems to indicate that there must be some basic factor in bacillus or host which prevents the development of sufficient antibodies to be of much practical value. Perhaps it may turn out that one must make an exception in the case of Calmette's new vaccine, which has, up to the present time, given quite significant results. But even if further trials substantiate all that has been promised by its use so far, it will nevertheless remain valuable as a preventive measure only, and its effectiveness will be measured by the extent of its application.

The one measure that has universally been admitted as being really successful in the treatment of tuberculosis is rest. In this category must be included not only rest for the body as a whole, but also all of those surgical methods which have been developed for obtaining comparative immobilization of various affected parts, such as ankylosis of joints, artificial pneumothorax, phrenicotomy and thoracoplasty. Certainly rest, both general and direct, has proved to be the one method that has been successful, and this success has probably been accomplished merely by aiding the normal processes of healing which the body possesses. Since extraneous methods have so far been much less successful in combatting tuberculosis than those processes which are inherent in animal tissues, it would seem that the general course of investigation, which has been mapped out and is being followed by the group of American investigators referred to above, is the wisest that can at present be undertaken. This course of investigation has, as its basis, the more complete and exact study of the fundamental problems of the biology and chemistry of the tubercle bacillus, and of the reactions of the animal tissues to the bacilli and various components of the latter obtained by chemical analysis.

Since so many cases of incipient tuberculosis are being healed without other intervention than that of rest and diet, it is obvious that the body's

tissues must be able, under optimal circumstances, to bring about the healing of tuberculous infections. Therefore, it seems logical to conclude that, if these reactions could be thoroughly analyzed, methods might be developed by which they could be stimulated or assisted. It has been with this point in view that the recent investigations, largely under the direction and with the assistance of the National Tuberculosis Research Committee, have been directed toward the renewed study of the character of the reactions of various tissues to tuberculosis. It is my purpose to review some of the more important observations which so far have been obtained in this connection.

From the standpoint of general discussion the reactions which occur in the tissues in tuberculosis may be conventionally divided into tubercle and allergy. These two reactions represent the primary and secondary responses of the animal body, and therefore must be considered with regard to questions of susceptibility and resistance. That tubercle is primarily protective in character cannot, I think, be denied; and yet it is quite obvious that the central localization of the bacteria, the surrounding tissue necrosis and the avascularity of the structure as a whole, are in many instances definite impedimenta to the effectiveness of any direct therapeusis. Nevertheless, it is quite possible that, if the primary capacities of these various cellular entities could be fully understood, tubercle might be placed more definitely in the category of protection and removed from that of a risk. In a similar manner tissue allergy must be approached. For here, as Krause has pointed out, we are also dealing with a protective reaction on the part of the animal organism, a reaction, however, which differs markedly from tubercle since it is the reaction of a prepared or sensitized animal. If the nature of the sensitization of the tissues, which is the allergic state, could be analyzed into factors approachable by external means, this bodily reaction might also be controlled and utilized as a protective and curative mechanism.

What then is the nature of tubercle? It is the characteristic anatomical reaction which is the primary response of the tissues of susceptible animals. The structure of tubercle is complex but it is built upon a simple basis; and the fundamental nature of this basic reaction is the presence of a single type of cell, the so called epithelioid cell. As Krause has so pertinently remarked: "Epithelioid cells, onion-layered, may alone be seen, as tubercle bacilli have disintegrated and disappeared; it is a tubercle. Tubercle bacilli may alone be present; it is not a tubercle.

Nor is it one if lymphocytes alone display themselves, or a giant cell alone." The usual arrangement of the tubercle is so well known that it is useless to dwell upon it in detail; it is only necessary to mention the various cellular components so that we may discuss their characteristics in turn. Epithelioid cells, the *sine qua non* of tubercle, giant cells and lymphocytes are the three types which we must consider as primary factors in tubercle-formation. The fibrous layer, developing later, and consisting of connective-tissue fibres and connective-tissue cells is definitely secondary in character. The presence of the granular leucocytes is an inconstant feature in the typical tubercle, but one which must be mentioned, especially in the light of conflicting opinions concerning their reactions.

Baumgarten is the outstanding figure in the study of the epithelioid cell, and his conception of the formation of these cells from connective-tissue elements *in situ* has remained the most probable explanation of their origin. Endothelium, blood-cells and wandering connective-tissue cells are the most important of the various sources, which have, from time to time, been advocated for the epithelioid cells; but Baumgarten's observations on the avascular cornea remain an outstanding argument for the formation of these cells from the fixed connective tissues. New light was brought to bear upon this question in 1923 when Dr. Sabin, in studying scrapings of a lymph node from a patient with tuberculosis, noticed small clumps of cells arranged concentrically and staining with neutral red, in a manner similar to the typical monocyte of the blood-stream. This observation formed the basis for the study of experimental tuberculosis later reported by Cunningham, Sabin, Sugiyama and Kindwall. These observers studied the reactions of various tissues in rabbits which had been inoculated with tubercle bacilli, and they found, in early uncomplicated tuberculous reactions, that there could be seen all transitions between a very primitive and undifferentiated type of cell and the typical epithelioid cell of tuberculosis. One of the stages observed was wholly similar to the monocyte of the circulating blood. Cunningham, Sabin and Doan had previously concluded, from other studies, that the monocyte develops from a stem-cell, present in the general connective tissues as well as in the haematopoietic organs, which they believe is also the parent cell giving rise to the lymphocytic and the granulocytic blood-cells. Thus it seems legitimate to conclude that the epithelioid cell of tuberculosis is derived from the monocyte, and that cells capable of producing monocytes, given the proper stimulus, are located throughout the

diffuse connective tissues as well as in the haematopoietic organs. These observations supply the missing link in the chain of evidence, and permit us to reconcile the conclusion of Baumgarten and that of the workers contending for the haemic origin of the epithelioid cells.

The concept that the epithelioid cell is derived from the monocyte has been supported by a considerable body of experimental data. Lewis and Lewis have found that typical epithelioid cells develop in tissue-cultures of whole blood, and, since all other types of cells apparently degenerate quickly, the relationship to monocytes seems quite definite. In reinfected animals Dworsky, Smith and Gardner have found evidence that the epithelioid cells of peritoneal exudates are derived from monocytes. Sabin and Doan have restudied the formation of epithelioid cells in rabbits, some of which were inoculated with living tubercle bacilli and others treated with phosphatide fractions obtained by chemical analysis. In both series they found evidence that the monocytes produced the epithelioid cells. Furthermore, in their recent observations Sabin and Doan have described the formation of great masses of monocytes and epithelioid cells in the connective tissues and have again supported the conclusion that these cells are derived from a primitive cell situated in the connective tissue.

As Krause has pointed out, the giant cell is in no sense a necessary accompaniment of tubercle. Nevertheless, its presence therein is sufficiently constant to be noteworthy and to require explanation. Its location is invariably among the epithelioid cells that are probably destined for disintegration, and in most instances tubercle bacilli can be demonstrated within its cytoplasm. The results of much of the recent work indicate that the giant cell is most probably related etiologically to the epithelioid cell in much the same way that the latter is to the normal monocyte; and hence represents, more or less, the terminal phase of an irreversible degenerative process.

In considering the relation to tuberculosis of the monocyte and the epithelioid cell, two questions present themselves, the answers to which would materially assist in the exposition of the nature of the tissue immunity in tuberculosis. Is it possible to utilize the monocytes of the circulating blood as an index of the state of tuberculosis? Can the production or activities of these cells be modified, and, if so, what effect would such changes have upon the progress of the disease?

The first of these two questions we can answer unequivocally in the affirmative. The fact that the monocytes are increased in tuberculosis

has indeed been known for many years, since it was reported as early as 1902 by Achard and Loeper, Halbron and others. The results of these workers were denied by so many others, and seemed so wholly unrelated to all general information regarding the disease that their significance was completely overlooked. In their original study of tuberculosis in the rabbit Cunningham, Sabin, Sugiyama and Kindwall found that the monocytes were markedly elevated in advanced and extensive tuberculosis. They also found that in many cases typical epithelioid cells, and all transition forms between the monocytes and epithelioid cells, appeared in the circulating blood. These observations have now been extended to other species.

Camp, Luton, Tompkins and Cunningham, in this laboratory, have found that there is likewise an increase in the circulating monocytes in the guinea pig (as well as an increase in both monocytes and epithelioid cells in the tissues with advancing tuberculosis). Furthermore, Cunningham and Tompkins have found, in cases of human tuberculosis, that the monocytes are definitely elevated, and that the number of these cells apparently parallels the curve of the clinical condition of the patient. It thus seems clear that the number of the circulating monocytes is roughly comparable to the extent of the tuberculosis, and, while we hope that this may serve as an aid in diagnosis and prognosis, we are nevertheless looking beyond this point and seeking for some method of controlling the production or activities of these cells, whereby their relation to susceptibility and resistance may be both accurately determined and eventually controlled.

If it is true that monocytes harbor the bacilli, can they be stimulated to increased cytoplasmic activity so that they can destroy the microorganisms? Or, failing this, can we reduce the production of these cells and thereby remove them as a potential danger to the host? Or is it possible to find substances which will either prevent the entrance of the bacilli into the cell, or which, also entering the cell, will bring about the destruction of the invader in its intracellular habitat?

The relation of the monocyte to the connective-tissue cells must be considered more particularly. In the first place, as pointed out above, much recent work indicates that there are undifferentiated cells, in the general connective tissues, which retain the capacity of producing monocytes when properly stimulated. These cells have been considered by Cunningham, Sabin and Doan as being of the same type as the so called reticular cells of the haematopoietic organs. On the other hand, for

many years there has been much discussion concerning the so called fibroblast of the connective tissues. Most of the earlier workers considered this cell as specifically the parent cell of the fibrous material of connective tissue. Recently Hertzler, Baitsell and Harrison have brought forward an imposing body of evidence to indicate that the formation of connective-tissue fibrils is dependent upon factors similar to those active in the clotting of blood and only secondarily dependent upon the action of cells. Whether there is any relationship between the reticular cell and the fibroblast, neither of which has as yet been accurately defined, is of course an important question. It has already been stated that there is evidence that the monocyte is derived from the reticular cell. It is also important to determine whether the monocyte has any relationship to the fibroblast. In this connection the recent observations of Carrel seem to be of the greatest importance. This observer has found, when cultures of monocytes are obtained from centrifugated blood, that these cells will finally become indistinguishable from cultures of typical fibroblasts. These observations have been applied to the subject of fibrosis of tubercle by Krause, who suggests that the peripheral layers of epithelioid cells may be under physical conditions which are comparable to those of tissue cultures, and that the production of fibroblasts may ensue in a similar manner. This is a most interesting concept and offers, in terms of the other considerations we are presenting, an opportunity for an approach to the study of tuberculosis which may prove of considerable value. Let us again refer to the character of tubercle. Tubercle is primarily a collection of epithelioid cells, and we always find degenerative changes beginning at the centre and progressing toward the periphery, while fibrotic changes begin at the periphery and progress toward the centre. Such a process might well be construed as indicating that the epithelioid cells nearer the centre of the tubercle are sufficiently injured to be incapable of undergoing differentiation into fibroblasts, whereas those on the periphery have retained this capacity. If it is admitted, for purposes of discussion, that the monocyte may become transformed into connective-tissue cells of the so called fibroblastic type, it still remains an open question as to the relationship which either of these cells bears to the production of fibrils. Nevertheless, fibrosis does occur at the periphery of the tubercle, and here also are developed long cells of the spindle-shaped, fibroblastic type. Consequently it seems legitimate, for the time, to accept as a working hypothesis the suggestion of Krause that the peripherally placed mono-

cytes may be an important element in this connective-tissue formation. With this in mind we must seek for methods whereby a greater number of these cells can be encouraged to undergo transformation into fibroblasts, or whereby this process may be initiated at an earlier period.

The relationship of monocyte to bacillus is also of very great importance. Many observers have described the phagocytosis of bacilli by mononuclear cells, and it has been customarily considered quite clear that these cells are capable of destroying the ingested microörganisms. This concept has been questioned by Pertik, who states that it seemed quite possible that the bacilli are not destroyed but instead multiply within the cells. This same possibility was advanced by Cunningham, Sabin, Sugiyama and Kindwall, and they further suggest that the bacilli may be able to change the cytoplasm of the monocyte so that its normal bactericidal powers are reduced or lost. Sabin and Doan have recently advanced additional evidence for this specific and peculiar reaction of the monocyte to the tubercle bacillus. Thus it seems that this reaction of monocytes to bacilli might result in assisting in the extension of the disease by protecting the bacilli against destruction and allowing them to multiply relatively unmolested within these changed cells. If we consider the possibility that even a small percentage of the monocytes are thus transformed into unresisting epithelioid cells, there might result a nice balance between extension and destruction, depending upon the ratios of resisting to nonresisting monocytes, and the number of bacilli destroyed or liberated by these respective types.

From the various studies to which we have referred above it seems probable that the monocytes develop from primitive connective-tissue cells. But from the monocytic stage there appear to be two divergent lines of further change or modification along which these cells may pass. I purposely call these lines of modification, and not lines of development, as one of them seems to be, very specifically, degenerative in character. In the first place, the monocyte may become the epithelioid cell as a result of infection by tubercle bacilli or the action of their products, and these in turn may undergo degeneration, thereby liberating their content of microörganisms. There are two direct results which may be noted when this change involves many individual cells; these are an increase in the number of viable bacilli and a production of areas of necrotic tissue. These changes must inevitably end in cavity-formation unless fibrosis intervenes at a sufficiently early period to prevent it. The other line of possible cellular change is in the direction of the fibroblast which must

be looked upon, at least for the present, as Nature's last line of defense. Thus from a single source, we have two possible outcomes; the one harmful, at least in part, and the other wholly beneficial to the bodily economy. Granting that the observations referred to above are correct, then our problem becomes the search for means to prevent or limit the course of monocytes toward degeneration and destruction, and to encourage their change into fibroblasts.

As mentioned above, much experimental work is in progress at the present time, which has as its aim the discovery of sufficient basic principles to control some or all of these factors. One such series of observations in particular must here be emphasized. These are the studies of Sabin and Doan on the effects produced by various chemical fractions of the tubercle bacillus on the reticular cell and the monocyte. They have found that the administration of a phosphatide fraction of the tubercle bacillus brings about a tremendous transformation of reticular cells into monocytes and monocytes into epithelioid cells. In this laboratory Schwartz and Cunningham have found that the smegma bacillus will also stimulate the production of monocytes and their transformation into epithelioid cells to a marked degree. Since both smegma and tubercle bacilli have fatty envelopes, these observations may indicate that this action of the acid-fast bacilli (to stimulate the production of monocytes and to effect their transformation into epithelioid cells) probably is resident in the lipoid substances present in these microorganisms and is therefore connected with cellular reactions to fats. It must also be considered that this reaction on the part of the monocytes may not be the result of the specific fat or fats contained in these microorganisms, but rather a reaction concerning the group of lipoid substances as a whole.

On the other hand, I would call your attention to the fact that the increase in monocytes is in no sense a specific reaction to the acid-fast group of microörganisms, but occurs in at least one other group of pathological conditions, namely, that in which the liver is injured. Jones and Minot found that the monocytes were increased in cases of infectious jaundice. Following this idea Holt ligated the common bile-duct in rabbits, and observed that after the operation there was a marked elevation in the monocytes. Further unpublished observations, made in this laboratory upon various other conditions which have in common the one factor of injury to the liver, show the same changes. There are several possibilities to be considered here, for we may either be dealing with the

direct effect of some component of the bile which is being absorbed, or these changes may be the resultant of some derangement of a normal liver function, or some product of liver degeneration may be the active agent in this connection.

In case we should find that behind these biological expressions (that is, changes in number and type of monocytes) there is, somewhere, a common factor, as, for example, some derangement of the local or general metabolism of fat, its identification would certainly be of enormous value, inasmuch as the specific control of any type of blood-cell production would be important in itself, and its application to tuberculosis obviously of immediate use.

Surrounding the tubercle there are always to be found numerous lymphocytes, or perhaps one should say cells which morphologically cannot be distinguished from the lymphocyte of the circulating blood, and the fact that these cells are so constantly present immediately raises the question as to what rôle they play in the various processes we have mentioned above. Do these lymphocytes, which form so characteristic a part of tubercle, exercise any protective function, and, if so, in what way do they carry out this reaction? Or are the lymphocytes merely an expression of the effect of some chemical substance which is present in particular concentration at the periphery of the tubercle? These two questions, together, suggest what seems to me to be a most important direction of approach to the study of tissue resistance or immunity in tuberculosis. As is well known, the large series of beautiful observations of Murphy and his collaborators at the Rockefeller Institute have shown quite conclusively that an increase in the number of lymphocytes is coincidental with an increase in resistance to tuberculosis. Murphy suggests that the lymphocyte itself is the factor which in some way supplies the resisting mechanism, but it must also be admitted that changes in the circulating or tissue lymphocytes may be due to some other factor which is the actual mechanism of resistance. It has often been demonstrated, in patients recovering from tuberculosis, that the lymphocytes are exceptionally high, and, in patients succumbing to the disease, that these cells are diminished in numbers. Webb, in particular, has emphasized this relationship. In their experimental work on the rabbit Cunningham, Sabin, Sugiyama and Kindwall found, in progressive tuberculosis, that the number of circulating monocytes increased and that of lymphocytes decreased. The reverse was true when the animals were recovering. These observations have been confirmed and extended

in the studies on the human cases in this hospital, and in the experimental studies on the guinea pig referred to above. We have found this relationship so constant that it can be utilized as a mathematical ratio to express the condition of the patient or animal. In guinea pigs succumbing to the disease it is remarkable to observe that the lymphocytes may, at times, fall to an exceedingly low level. This is particularly true in those animals in which intoxication develops relatively slowly, an observation which may well indicate that the power of the lymphocyte-producing tissues has been profoundly depressed. Tuberculosis of lymph nodes is a well-known and common occurrence. If lymphocytes, in themselves or by reason of their secretions, were protective against tuberculosis, we should expect the reverse. If, on the other hand, there is some factor which depresses the lymphocytes and stimulates the monocytes, we could understand why tuberculosis of lymph nodes, with the production of great masses of localized epithelioid cells from the common stem-cell of the lymphocyte and the monocyte, might readily take place.

The same line of reasoning may be followed with regard to the great susceptibility of guinea pigs which have an unusually large number of circulating lymphocytes. With this interpretation the decrease in circulating lymphocytes, in progressive tuberculosis, would be the result of an increase in this unknown factor and not directly the cause of the failure in resistance. This is the theory which we are, at the moment, utilizing as a basis for further studies, inasmuch as, if such a factor be present, it may in turn be capable of analysis, and if capable of analysis may result in definite advances from the protective side. Nevertheless the great importance of Murphy's observations must not be lost sight of, and every effort must be made in the study of ways and means for increasing lymphocytopoiesis as a method of protection in tuberculosis.

Again the question must be raised as to whether the peripheral location of the lymphocytes may be taken as an indication that they are a stimulating or a controlling factor in the transformation of the monocyte into the fibroblast. Or is it perhaps a case of monocyte and lymphocyte reacting upon each other and upon the plasma to bring about the production of the connective-tissue barrier? Should this hypothesis prove to be correct, some method of accelerating the production of fibrosis might be developed.

The granular leucocytes are not a part of the true anatomical tubercle. According to many authors there is a short period immediately following

inoculation when polymorphonuclear leucocytes (especially of the neutrophilic type) collect about the bacilli, phagocytize them, and then either wander away or degenerate. This early reaction has been recently emphasized by Baldwin, Petroff and Gardner as follows: "A small amount of serum exudes from the nearby capillaries and a few white blood corpuscles migrate into the air spaces. The reaction is transitory, however, and usually subsides within the first twenty-four hours." And, in discussing the early stages of primary infection of the peritoneal cavity, they say; "The peritoneal cavity offers more ideal conditions for such observations as the injection of suspensions of organisms provokes the formation of cellular exudate, portions of which may be withdrawn at serial intervals for study. Intraperitoneal inoculation in the guinea-pig demonstrates that within the first eight hours tubercle bacilli may be ingested by either the eosinophile or neutrophilic polynuclear leukocyte or by large mononuclear cells, but that thereafter the latter cell plays the chief rôle in phagocytosis."

Resistance in tuberculosis has been studied in great detail, not only from the standpoint of the formation of tubercle, but also from many other points of view. From the mass of evidence collected it has gradually become clear that, while there are several reactions which may be traced to analogous types in other immunological studies, nevertheless the most remarkable interpretation of variations in resistance is that they are dependent directly upon cellular reactions. That is to say, notwithstanding an absence of circulating antibodies a high resistance to tuberculosis is frequently evident, while, with such antibodies present in comparatively high titre, no increased resistance is observable (Krause). Therefore, in the study of immunity to tuberculosis, one turns again to tissue reactions and here, in addition to those which occur in the primary infection, that is, formation of tubercle, there is a characteristic group of changes following reinfection. For this tissue reaction to reinfection, which is dependent upon tissue sensitization, Pirquet coined the word *allergy*. The phenomena seen in reinfection in tuberculosis may be primarily attributed to a hypersensitive state on the part of the tissues, and this hypersensitive condition has been called the *allergic state*. Therefore our first consideration is, wherein lies the difference between the primary and secondary responses of the animal to tuberculous inoculations. It is broadly stated by saying that allergy partakes more of an acute inflammatory reaction than does that which occurs in tubercle. The course of events in reinoculation of the guinea pig has been beauti-

fully analyzed by Krause and Peters and may be briefly reviewed as follows: When a sensitized guinea pig is given a subcutaneous inoculation of virulent tubercle bacilli, an acute inflammatory reaction develops at the site of the inoculation within twenty-four to thirty-six hours. This process becomes fulminating in character and ends either in rapid subsidence or in ulceration. If ulceration occurs, healing takes place quite promptly. Following either healing or subsidence of the acute inflammation, small, soft, localized tubercles develop quite promptly in the same region. As a rule there is some temporary improvement in the condition of the animal.

In general, studies on reinfection and hypersensitiveness have taken two directions. They have, in the first place, been concerned with the utilization of the secondary inflammatory reaction, which apparently results in a diminution of the primary lesion, as a possible method of indirect therapeusis. Vaccines have been given in the form of small doses of virulent or larger doses of nonvirulent bacilli, with the idea that, by increasing the local reactivity of tissues, more rapid healing might be promoted. One such series of studies involves the use of autogenous pleural exudate to stimulate resorption and healing. Again, exercise in carefully graded amounts, together with deep breathing, has been advocated in order to facilitate absorption of tuberculous products and thereby produce an increased allergic response. These, and many other similar attempts, have constituted a direct utilization of this reaction as a therapeutic measure. As is well known, they have resulted in some cases in temporary improvement, and in others in dangerous and even fatal sequellae. This does not necessarily invalidate the hypothetical basis on which such treatments have been advocated, but merely indicates that exact knowledge with regard to this reaction is insufficient to permit of its practical application.

On the other hand, numerous observers have been concerned with studying more exactly the tissue reactions as exemplified by the various cellular entities. This work has been recently reviewed by Baldwin, Petroff and Gardner, and they furthermore give details of their own careful study of the cytology of the exudates occurring in the peritoneal cavity following reinfection. Specifically, they have found that when guinea pigs are reinfected with tubercle bacilli, given intraperitoneally, the following course of events takes place in the peritoneal exudate. During the first twenty-four hours, there is a marked outpouring of polymorphonuclear leucocytes which phagocytize the bacilli to some

extent. These cells are not the primary phagocytic defense; they function rather by means of their ferments. By the end of the first twenty-four hours, monocytes appear and proceed to ingest large numbers of the microörganisms. As the condition progresses the monocytes increase in number, but there are apparently few or no lymphocytes in the exudate. If the process is sufficiently severe to end in the death of the animal, the lymphocytes do not appear in any marked numbers, but in cases in which the reaction subsides, coincidental with an improvement in the animal, the curve of the monocytes falls and that of lymphocytes shows a progressive rise. These observations therefore are quite in accord with the changes already discussed as taking place in the formula of the cells of the blood. This becomes clear when it is recalled that in the formation of primary tubercles, there is, after two or three weeks, evidence of a mild inflammatory reaction in the periphery of the tubercle.* This probably indicates that sensitization has taken place and that in the extension of the local process there is a definite secondary inflammatory reaction. In generalized tuberculosis, therefore, the more or less recurrent periods of exacerbation and improvement may well be waves of allergic reaction due to graded autoreinoculation.

Finally, in review, the considerations which must particularly occupy our minds at the present time are the following: Is there any mechanism whereby we may be able to unravel the basic reactions which nature is using in the healing that so often occurs in tuberculous processes? To do so, we must analyze more carefully the primary reactions of the individual cells concerned in tubercle and allergy; and it is clear that the most important of these cells are the monocytes and the lymphocytes. Regardless of the controversies, which are active at the present time concerning the etiology and physiology of these cells, the observations which point to their being concerned in tissue immunity in tuberculosis are very definite, even if not as yet very extensive. It is, of course, important that further work should be done in attempting to reach the final truth with regard to the nature and origin of these cells and their developmental potentialities. While such studies are important, in order to understand the significance of their occurrence in tuberculosis, nevertheless we think that it may be accepted as definitely settled that these cells do represent, to a considerable degree, specific measurements of the progress and regression of the disease.

There are collateral issues to these primary concepts, which may or may not be fully established with later work. Among these must be

noted in particular the question as to whether the physiological limitations of the monocyte permit its acting as a culture medium for the invading microörganisms. It also remains to be determined whether the lymphocyte is primarily engaged in some specific manner in resisting the tubercle bacillus or whether the marked fall in lymphocytes, in advanced tuberculosis, is the resultant of some toxic agent liberated by the disease and conditioning the production of these cells. These suggestions must be considered merely as stimulating ideas, upon which future work can be based, and not accepted as proved conclusions. With this in mind, it seems legitimate to assume that the hope for a more rational handling of tuberculosis in the future probably lies in a careful study of tissue immunity. It is, of course, always to be desired that a direct path will be found which will lead us to specific treatment, but the innumerable failures, which have been met with in the past in experimental work directed toward this end, have made the medical profession exceptionally cautious in giving heed to new therapeutic measures. Until such a direct cure has been found it seems wisest for us to concentrate on the investigation of primary tissue reactions in order that we may profit by the fact that nature undoubtedly has the power of healing tuberculous lesions. By a wider knowledge of these processes we may be able to assist in their increased success more effectively than we can at present.

MODERN CONCEPTS IN THE PATHOLOGY OF TUBERCULOSIS

An Analysis[1]

MAX PINNER

Rien n'est plus puissant que l'influence du langage; et l'on sait que les déterminations erronées, les définitions equivoques et les faux aperçus appellent à leur suite l'erreur, la confusion et les fautes les plus graves, surtout dans les sciences qui, comme la médicine, offrent des applications pratiques.—G. L. Bayle, 1810.

I. TERMINOLOGY

In an attempt to analyze the progress of pathologico-anatomical studies in tuberculosis during the last few years, one is struck with a curious national difference in regard to the basic morphological interpretation and the theory of pathogenesis. The apparently essential divergences of the different schools are based on characteristically different methods of work and observation. The French contemporary school, represented by Letulle, Sergent, Bezançon, Ameuille, etc., following in the footsteps of their great masters, Bayle and Laennec, have in recent years elaborated in great detail the more or less finished product of the tuberculous infection; they have traced with minute accuracy the morphology which underlies the various clinical manifestations. The German school, represented by Albrecht, Ghon, Aschoff, Ranke, Puhl, Schürmann, Huebschmann, true to the tradition of German medicine, has developed concepts of generalization founded both on extensive morphological observations and experimental data, with the addition of a definite purely speculative element. The American work, as represented by Prudden, Miller, Krause, Opie, Gardner, was almost exclusively of an experimental nature and the anatomical structures "in their functional relations" (Krause) have here been of primary concern. It is not surprising, then, that the various concepts are at great variance considering the fundamental differences in the mode of attack; it is astonishing,

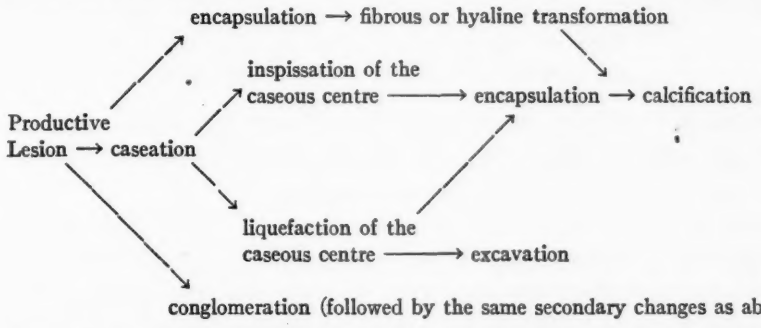
[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

however, that there has not been more of an exchange of scientific ideas between the schools. How little in fact we have had of this is clearly demonstrated by the fact that each school uses at the present time so different a terminology as to prevent a fruitful exchange more effectively than do the mere linguistic difficulties.

First it may be mentioned that there has been a considerable amount of discussion on the proper name for the disease as an entity. Orth, and after him with more emphasis, Aschoff, have pointed out that tuberculosis is an unsuitable name, since extensive lesions, caused by Koch's bacillus, may not contain a single tubercle, this latter term being understood in its etymological significance, that is, a small nodule, and one might as well call syphillis *gumma disease*, or *gummatosis*, since some of its pathological products are characterized by gummatous formations. Aschoff prefers, therefore, to speak of phthisis, the phthisis bacillus, etc., and wishes the term tuberculosis reserved for the lesions of the type of granulation tissue only. It is true enough that from this standpoint of judicious linguistic criticism, tuberculosis is an ill-chosen term, but it is equally true that not by far all the lesions, due to Koch's bacillus, are characterized by phthisis, that is, consumption. Since neither term, accordingly, is descriptive for the whole array of lesions, the name *tuberculosis* will probably survive on the strength of usage and tradition. The exactly opposite attitude is represented by Krause, who proposes to name tubercle "all anatomical response to tubercle bacilli." Here the original meaning of tubercle is deliberately disregarded and in a strictly etiological sense the *anatomical* terminology is derived from the *bacteriological* nomenclature.

All schools are well agreed on Laennec's main statement, that in tuberculosis there exist two fundamentally different tissue alterations, *tubercules* and *infiltrations*, productive and exudative processes, although their relative independence and their pathogenetic mechanism are points of controversy. It appears from the literature that the terms productive and exudative, as applied to tuberculous alterations, are not always used in exactly the same meaning. Since both lesions involve the rapid accumulation of cells, they both necessarily involve "proliferative" processes, if one does not assume that the cells involved are exclusively of haematogenous origin. Both exudative and productive processes are proliferative, and the correct antonym is not *proliferative-exudative*, but *productive-exudative*. The essential characteristic of the two types of lesion is as follows: In the productive tubercle a *new tissue*

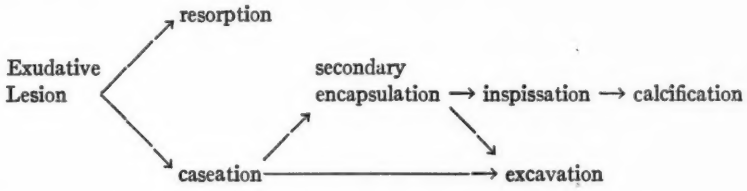
is formed, consisting of epithelioid cells and a varying number of lymphocytic, leucocytic and giant cells; this new formed granulation-tissue contains a definite reticulum; it always shows in its further development some fibroblastic cells in the peripheral zone; which may lead to a more or less competent capsule-formation. If the tubercle caseates, it is primarily the new-formed granulation-tissue which becomes necrotic and not the tissue of the organ involved. When cavitation occurs it is the granulation tissue which is expelled and not the parenchyma; this latter is pushed to the side as the tubercle grows, and it may necrotize through *secondary* changes. The possible modes of evolution are shown in the following schema:


encapsulation → fibrous or hyaline transformation
inspissation of the
caseous centre → encapsulation → calcification
Productive
Lesion → caseation
liquefaction of the
caseous centre → excavation
conglomeration (followed by the same secondary changes as above)

There is some roentgenological and clinical evidence that productive lesions may heal by resorption (Amberson), but the writer does not know of any convincing proof for this possibility.

The exudative lesion does not develop a new tissue but an exudate, consisting of various amounts of plasma proteins and cells, both of histiocytic and haematogenous origin; this exudate is poured, as it were, into the normal tissue, it infiltrates the latter, it does not replace it. It is a process which involves the internal surface of the lung and not its framework. This can best be studied in pulmonary lesions: One finds here that, not unlike in a pneumococcic pneumonia, the air-spaces are filled with the exudate and the normal structures of the lung, such as alveoli, bronchi, vessels, are not disturbed beyond the existence of oedema and secondary inflammatory changes; the structural relation of the framework—as revealed by selective stains for elastic fibres—is unaltered. When this lesion undergoes caseation, the exudate *and* all the cellular elements of the involved organ caseate, leaving only the resistant elastic fibres intact; if cavitation occurs the necrosed exudate *and* the necrosed part of the organ are expelled.

Exudation does not necessarily mean that all the elements are derived from the blood; the cells contained in the fluid vehicle may well be proliferated alveolar, adventitial and fixed wandering cells. The points of difference are not in the *derivation* of cells, but in the fact that the productive lesion grows by intussusception (expansive growth), that it forms a true tissue; while the exudative lesion expands by infiltration and forms not a tissue, but an exudate. The fate of an exudative process is as follows:



The marked differences between exudative and productive processes are clearly shown again in Miller's studies on the behavior of the reticulum, particularly during the process of healing.

The profound confusion in the terminology will be realized best after the perusal of table 1, which represents an attempt to correlate the various terms. It will be seen, that, for instance, the German *Miliartuberkel* is a vastly different thing than the modern French *tubercle miliaire*, or Krause's *tubercle;* that *nodule tuberculeux, nodöse Phthise* and *nodular tubercle* have not much more in common than their etymology.

It is not intended to suggest here an agreement on or a standardization of terminology. This little compilation, which by its very nature is objectionable and incomplete, may, however, serve a similar useful purpose as does a dictionary. How much a better terminological understanding is needed was well realized at the Washington conference, when the discussion after Dr. Krause's paper was more motivated by mistaken terms than by differences of facts and observations.

The table presented here needs comments on various points. Laennec's *tubercules miliaires*, "gray, semitransparent, frequently not quite round, adhering firmly to the pulmonary tissue, growing by intussusception and pushing the normal tissue aside," may be interpreted as miliary (nodular) tubercles. That Laennec conceived them as these productive formations is further supported by the following facts: He described correctly their further development: caseation, conglomeration; and he emphasized, by his very terminology, their essential differ-

ence from the other type of tuberculous lesions (infiltration). Letulle, and with him numerous French pathologists, however, interprets

TABLE 1

LAENNEC	MODERN FRENCH (LETULLE)	MODERN GERMAN (ASCHOFF)	A. K. KRAUSE
Infiltration tuberculeuse*	Tuberculose pneumonique Tuberculose infiltrée	Exsudative Phthise	Non-nodular tubercle
1. Infiltration grise	Bronchopneumonie caséeuse	Lobulär käsige Phthise	
2. Infiltration jaune	Pneumonie caséeuse lobaire	Lobär käsige Phthise	
	——		
	(Tubercule massive) (Hanot) (Tubercule pneumonique) (Grancher) (Tubercule aggloméré) (Charcot)		
3. Infiltration gelatiniforme	Splénisation tuberculeuse	Exsudative Phthise (glatte Pneumonie) (Virchow)	
	(Splenopneumonie) (Grancher)	(Desquamativ-Pneumonie) (Buhl) Probable examples: (Epituberkulöse Infiltrate of Eliasberg) (Infraklavikuläre Infiltrate of Assmann)	
Tubercule miliaire	(Bronchio-alvéolite)	Azinös-exsudative Phthise	
Tubercule crujaune	Nodule tuberculeux, tuberculose nodulaire	Lobulär-exsudative Phthise	
Tubercule enkysté	Tubercule enkysté	Nodös-indurierte Phthise and encapsulated exudative foci	
Granulation tuberculeuse	Tuberculose folliculaire	Productive Phthise	Nodular tubercle
Granulation miliaire	Follicule tuberculeuse	Acinös-produktive Phthise und Miliartuberkel	

* It is apparent from Laennec's description that his three types of infiltrations correspond to different stages in the development of the lesion, the gelatinous infiltration being the youngest and not yet caseated form, and the yellow infiltration being the completely caseated lesion. The gray infiltration, probably, is an intermediate stage, although it has been suggested that it may correspond to dense fibrosis, owing to Laennec's words that it may at times have the consistency of cartilage. On the other hand, this assumption is unlikely on account of Laennec's statement that the gray may be transformed into the yellow infiltration.

Laennec's *tubercles miliares* as miliary pneumonic tuberculous areas, probably chiefly on the strength of two statements in Laennec's descrip-

tion; that they are the most common form of tuberculous matter in the lung, and that they are sometimes a little angular. It appears to be a safe supposition that Laennec, not having the advantage of microscopical studies, interpreted in fact several lesions as *tubercules miliaires;* namely, the typical miliary tubercle of interstitial growth, the productive (nodular) lesion—beginning after a bronchogenic infection—in the alveoli (*azinös-produktive Herde* of Aschoff), and occasionally, too, the earliest inception of a pneumonic focus, (*azinös-exsudative Herde* of Aschoff). In the French interpretation of Laennec, he would not have seen the cellular tubercle at all. His *tubercule granulaire,* which in his own words is identical with the rare variety of tubercles described by Bayle as *granulation miliaire,* is unanimously recognized as a fibrotic miliary tubercle: *vieilles lésions folliculaires, plus ou moins transformées en petits fibromes lamellaires* (Bezançon and Braun), they are *une fin du tubercule miliaire* (Letulle). Laennec, however, believed that they may caseate in the centre (an observation which caused him to recognize them properly as tuberculous lesions). That his *tubercule granulaire* may caseate is usually believed to be a mistake of the master; he is supposed to have erroneously inversed the order of occurrences. It is, however, quite possible, too, that Laennec described as *tubercule granulaire* both fibrotic tubercles and epithelioid-cell tubercles; for the latter his description of their further fate would be perfectly correct. One cannot doubt from Laennec's writings that he has observed and correctly interpreted both the development from the epithelioid tubercle to conglomeration, caseation, encapsulation and cavitation and the consecutive occurrences in the evolution of the exudative (non-nodular) lesions; he realized their essential morphological differences and (probably the most admirable part of his studies in tuberculosis) he recognized their pathogenetic unity. It is only the use of his terms which causes, retrospectively seen, some controversy. If (which is more than likely) he confused at times the incipient nodular and the incipient non-nodular lesion from their gross appearances, he failed no more than any modern pathologist, who cannot always make the correct distinction without microscopic studies. More or less the same is true of his *tubercule cru* and his *tubercule enkysté.* Each may represent a development in either the productive lesion (*nodöse Herde, induriert-nodöse Herde resp.,* Aschoff) or the exudative type (*lobulär käsige Herde,* with and without secondary capsule formation, Aschoff). The latter is probably only true for the relatively rare, isolated and scattered foci.

This rather lengthy discussion of Laennec's observations and terms bears more than mere historical interest, since the modern French school of pathologists, in fully justified admiration of its master, attempts to adhere very strictly to his terminology. More than this, their studies appear at times to tread the dangerous path of medieval philosophy, when the words of the master, and not facts were matter of discussion. A striking example of this may be found in this instance: Letulle, obviously, in order to adapt his classification to Laennec's, introduces besides *tuberculose folliculaire* and *tuberculose infiltrée* a third class, that of *tuberculose nodulaire*, comprising all that Laennec termed *tubercule cru*. Letulle is, of course, well aware that both productive and exudative lesions are thus thrown into one rather unnaturally and ill-defined group. A similar group is found in Fränkel-Albrecht's classification, under the name of *nodöse Tuberkulose*, or, *grobknotige Tuberkulose;* but in the subsequent work of Nicol from Aschoff's institute this group was properly divided into its two morphogenetically different components of *nodöse Phthise* (that is, productive) and *lobulär-exsudative Phthise* (that is, exudative). It may be well to stress here the fact that not every lesion which appears macroscopically as a "nodule" is a productive process; even well-defined and encapsulated processes may have arisen by exudative alterations; a proper differentiation in the fully caseated stage can only be made by a study of the elastic structures.

Since in table 1 a correlation, or translation, as it were, is given for the various terminologies, it was unavoidable to introduce in the different columns terms which, seen from the individual classification, do not belong there. In order to represent the classifications properly, they are given here (tables 2 and 3) without the somewhat strained attempt at correlation. (See page 608.)

The emphasis in Aschoff's classification rests on two distinct points. First, it is pointed out that the productive and the exudative lesions have a different evolution, which is clincially and therapeutically most significant and that a clinical differentiation of the types is possible. Secondly, it is shown that any pulmonary tuberculous infection (with the exception of the haematogenous miliary tuberculosis) begins and propagates *within* the ramification of the bronchial tree; hence the universal application of the word *acinus*[2] for the individual entity of the lesions.

[2] Aschoff's *acinus* is, except for some minor details, identical with Miller's *primary lobule.*

TABLE 2

Aschoff's Classification

QUALITY	MORPHOGENESIS	FATE (AUSGANG)	SECONDARY CHANGES	EXTENSION
Productive phthisis	1. Interstitial form = phthisis tuberculosa interstitialis = miliary tuberculosis 2. Acinous phthisis 3. Acinous-nodose phthisis 4. Cirrhotic phthisis	Induration (fibrosis) or Caseation	Chronic ulcerative Chronic cavernous	Apical Descending Cranial Caudal
Exudative phthisis	1. Acinous-exudative or caseous phthisis 2. Lobular caseous phthisis 3. Lobar caseous phthisis (pneumonia)	Encapsulation or Liquefaction	Acute ulcerative Acute sequestrating	

TABLE 3

Letulle's Classification

I. Tuberculose pneumonique = tuberculose infiltrée
   1. Tubercule miliaire = bronchio-alvéolite
   2. Pneumonie caséeuse (beginning with "hépatisation fibrino-leukocytaire" and ending in "necrobiose caséogéne")
   3. Bronchio-pneumonie tuberculeuse (peribronchial infiltration, which unlike 2 is always associated with interstitial exudation)
   4. Splénisation tuberculeuse (gélatiniforme) (cellular exudate, which undergoes a characteristic "necrose vitrifiante" a "procédé necrobiotique précaséeux")

II. Tuberculose nodulaire
   1. Granulations multifolliculaires
   2. (Boncho)-pneumonie caséeuse (often with capsule-formation)

III. Tuberculose folliculaire = granulation tuberculeuse (its unit being always the "follicule primitif"). Tuberculose miliaire aigue (d'Empis) = granulie pulmonaire

A judicious application of modern therapeutics in tuberculosis, rest, exercise, surgical and specific treatment, necessitates a diagnosis which includes more details than the extent of the lesions and the recognition of cavities. Only by judging correctly the *probable and possible natural fate* of an individual lesion—resorption, excavation, encapsulation and fibrosis, propagation by circumfocal progression, or by bronchogenic spread—is a rational treatment possible. It does not belong here to enter into the discussion whether immunological or anatomical studies

are more likely to create a safe basis for such judgment. But it is obvious that a differentiation into predominantly exudative and predominantly productive lesions will always be a most significant factor in prognostication. Various authors hold that the differentiation into exudative and productive lesions is artificial, or even impossible, or that it is insignificant, since the two processes are almost always found in close combination. As far as one individual lesion is concerned it appears that (at least in the lung) the differentiation can always be made as soon as the lesion can be diagnosed as tuberculous. The very frequent combination of the lesions is never one of inseparable mixture, but is always of the order of a juxtaposition. In other words, close as the association may be, there always exists a dividing line, A productive focus surrounded by an exudative margin obviously has another significance than an exudative focus surrounded by productive tubercles.

When for practical reasons the modern work emphasizes particularly the qualitative differences in the various pathological processes, this trend of thought is not by any means to be understood as a reversion to the dualistic concept of Virchow's time. Laennec laid the permanent foundation for tuberculosis as a pathological entity. Koch proved its etiological unity and Baumgarten, against the purely morphological conceptions of Virchow, demonstrated beyond doubt the histological and pathogenetic unity of the protean lesions occurring as a response to the tubercle bacillus. This fundamental work of Baumgarten appears, unfortunately, to have left less of an impression on modern writers than his now generally discarded theory of the intrauterine transmission of the virus. Still, it is due to his admirable studies that the unitarian concept of tuberculosis is now so safely founded that the modern work can (without falling back into Virchow's dualism) elaborate the qualitatively different processes in order to offer the clinician directions for therapeutic action. The emphasis in scientific work changes according to practical needs. At a time when it was conceived that the worst that may happen to a phthisic was to become tuberculous, when scrofulosis was more of a battlefield for controversial opinions than a well-defined disease, Baumgarten rendered the greatest possible service to the investigative work in tuberculosis by proclaiming its morphogenetic unity, by stating, after more than ten years of experimental and anatomical studies, that "the miliary tubercle of pulmonary parenchyma is, histologically considered, nothing else but a miliary chronic caseating pneumonia, and the chronic caseating pneumonia is, histologically

analyzed, nothing else than a genuine tuberculous process of the pulmonary parenchyma." But, to-day, when the concept of the histogenetic and etiological unity of phthisis, tuberculosis and scrofulosis is an undisputed possession of all, progress lies in the finer differentiation within the entity.

Unlike the general agreement that exists in regard to the etiology and to the existence of two characteristically different types of lesions, one finds open disagreement in regard to the functional significance, and to the determining factors for the dual tissue alterations. It is obviously of greatest importance to know what factors determine the development of an exudative or of a productive lesion. The following theories have been propounded for an explanation:

1. The natural response of the noninfected, nonallergic organism is an exudative lesion, that of an allergic organism is a productive lesion. (Aschoff and his school.)
2. The natural response of the noninfected, nonallergic organism is a productive lesion, that of an allergic organism is an exudative lesion. (Modern American school.)
3. The natural response of an noninfected, nonallergic organism is an exudative lesion, quickly followed by productive lesions, surrounding the first focus. Then follows a stage in which the body is hypersensitive to the tubercle bacillus and its products, characterized by exudative lesions, caseation of lymph nodes and marked circumfocal inflammation; this is followed by a stage of relative immunity, with predominantly productive and localized lesions without lymph-node involvement. (Ranke and his followers.)
4. The response to an endobronchial infection is an exudative lesion; the response to an interstitial deposition of bacilli is a productive lesion. (Modern French school.)

This brief and somewhat schematic representation cannot do full justice to all the attempts at explanation, and it leaves out some more or less pertinent details in order to show better the profound differences of concepts. Almost all authors agree that, besides their chief points, some incidental factors are operating, modifying to various extents the basic rule. *Mutatis mutandis*, a larger dose of bacilli, greater virulence of the microörganisms, more or less clearly defined conditions of lowered "resistance" would tend toward the development of exudative lesions. The influences that the physiological tissue changes brought about by increasing age, those due to chronic irritation, and the one brought to bear by mixed infections, exert on the development, have been variously considered.

It is not intended to offer here the representation of *one* system. The writer intends to set forth the arguments in favor of each concept as represented by the respective authors. It will be necessary for this purpose to dwell somewhat at length on two phases of tuberculosis, which offer particularly elucidating conditions and which have not met with much attention in the recent American literature: the primary complex and miliary tuberculosis. In the former, considering only the *pulmonary* primary complex, is exemplified the evolution of an endobronchial lesion in virgin soil; the latter permits the study of the development of interstitial infections in a more or less allergic body.

II. THE PRIMARY COMPLEX

Parrot was the first to draw attention to the fact that, whenever tuberculous lesions are found in the tracheobronchial lymph nodes, a parenchymatous focus can be detected in the area drained by these structures. Küss in his classical thesis and, following him, Albrecht, Hedren, Ghon, Ranke, and many others have studied in detail the localization, the pathologico-anatomical structure and the development of the primary focus in man. If far-reaching conclusions be drawn from this anatomical entity, convincing proof must first be brought in evidence that it is possible to recognize with a fair degree of certainty the anatomical alterations brought about by the tubercle bacillus at its portal of entry into the human body. Such proof would necessarily involve the demonstration that the first anatomical response to the tubercle bacillus is structurally different and distinguishable from any later manifestation of the disease. The anatomical characteristics of the primary focus (*chancre de primo-infection* of the French authors, *focal tuberculosis* of Opie), when met with in the lung (but *mutatis mutandis* the same in any other organ), are as follows: It is a small exudative focus (miliary bronchopneumonia) which undergoes rapid caseation, but the exudative origin of which can be proved beyond any doubt, even after complete caseation has taken place, by the demonstration that in the caseated area the elastic-tissue structure of the pulmonary parenchyma is preserved, and frequently astonishingly well and completely. A productive process would by its very nature push the elastic-tissue network to its periphery; the exudative process infiltrates the meshes but does not disturb the frame. This caseated centre is surrounded in its early development by productive tubercles, which probably produce the inner "specific" capsule of the later stage, consisting of broad hyalinized connective-tissue fibres; the

outer nonspecific capsule consists of ordinary fibrous tissue and is usually explained to be the product of the nonspecific inflammatory reaction surrounding the active primary focus. The focus, capsule and caseous centre, are frequently infiltrated with lime salts, while complete petrifaction and not infrequently true bone-formation results. If a primary focus is found in a state of more or less complete anatomical healing, it is sharply defined against the normal lung tissue, which shows none of the secondary changes encountered almost regularly around healed foci of reinfection, such as thickening of the alveolar walls, altelectasis, massive anthracosis, emphysema. A further most important characteristic is the never absent affection of the draining lymph nodes, which results in a similar way in an extensive caseation surrounded by a fibrous capsule. This lymph-node focus (there may be two or three in the same drainage system) undergoes the same retrogressive changes as does the parenchymatous lesion. This primary lymph node has a totally different appearance, macroscopically as well as microscopically, from the lymph-node foci found in the tributary lymphatics of later tuberculous processes: complete caseation surrounded by a dense capsule in the primary focus; sluggish, multiple productive tubercles with varying extents of central caseation, and without a definite capsule in later manifestations. In the former case, the structure of the remaining lymphatic tissue is not materially changed, in the latter process hypertrophic adenitis and hyalinization of some of the reticular elements is the rule. Mention may be made, too, of the characteristic localization of the primary focus: it is always close to the pleura and rarely at the apex; in other words, the best aerated parts of the pulmonary parenchyma are most frequently affected.

Studies on thousands of cases have again and again established the fact that the primary complex, composed of a parenchymatous focus and a similar one in the regional lymph nodes, is structurally characteristic for the primary infection, and for the primary infection *only*. In a recent study, Schürmann published his findings in regard to the primary complex in a consecutive series of 1000 necropsies. In 889 of these cases tuberculous lesions were found, and in 855 of these, that is, 96.17 per cent, a primary focus was identified. It is of particular interest for the point in question here, that in 37.98 per cent of the cases only *one* lesion was demonstrable which had invariably the characteristics of the primary focus. Zarfl seems to have been the first author who had the good fortune to find in a human being, a 23-day-old child of a tuberculous

mother, a quite young primary focus. It was a focus of the size of a hempseed, yellowish-grey near the anterior surface of the left upper lobe, surrounded by perfectly normal lung tissue. The microscopic picture was typically that of an early tuberculous pneumonia (*broncho-alvéolite* of the French authors); namely, oedematous alveolar walls, and the alveoli themselves filled with a cellular exudate containing innumerable tubercle bacilli. This was the only tuberculous focus that a careful search revealed in this body. The reproductions of the microscopical section bear a striking resemblance to the picture that is found in Baldwin, Petroff and Gardner's book, representing an "early primary pulmonary tubercle" in a guinea pig (p. 94). Ghon and Roman published essentially the same findings concerning a boy, 5½ months of age: "typical fibrinocellular pneumonic foci with more or less pronounced caseation in the central parts, without demonstrable tubercles and without giant cells, rich in tubercle bacilli and free from other bacteria. There is no connection with vessels which could have aroused the suspicion of a hematogenous origin." The importance of the primary complex as a source for later infections is still a mooted question. Opie showed recently that the primary focus is frequently sterile, while coexisting apical lesions contain tubercle bacilli. He concluded that the apical and progressive lesions must, therefore, be caused by exogenous reinfection. Ghon, however, pointed out, years before Opie's report, that, regardless of the anatomical condition of the primary focus, its draining lymph nodes frequently show active disease, and that the entire chain of lymph nodes up to the venous angle may be diseased. In this way there may occur a slow feeding of tubercle bacilli into the blood-stream. This "endogenous, lymphoglandular reinfection" may well account for bacilliferous foci in the presence of a sterile primary focus.

The experimental infection of animals permits the study of the response of the body to the introduction of tubercle bacilli at any given interval after the infection. Great care must be taken, however, to study really the first lesion and not a secondary metastasis. Krause has pointed out that any process observed about two weeks after the infection may be influenced by the allergic condition. In regard to the pulmonary primary focus, the intratracheal infection is likely to afford the best opportunities. Bezançon, Brunel and Serbonnes have used this method; the early lesion, which they reproduce in print, shows clearly a fibrinocellular exudate filling the air-spaces, the alveolar walls

being swollen and oedematous; there are no giant cells, no granulation tissue, in brief, no sign of a productive inflammation. Baldwin and Gardner, in the course of similar studies, made identical observations; their photomicrographs show the same conditions as mentioned above. But, their interpretation differs. Since the first exudative reaction is followed by "the formation of a mantle of granulation tissue," they consider the lesion as productive. Gardner, in later studies on resorption of tuberculous infiltrations in the lung, showed convincingly that the resorption leaves a materially unaltered framework; it is not conceivable that granulation tissue after its resorption (if such may occur) could leave the elastic structure undisturbed. It is a common experience that, wherever tuberculous granulation tissue grows, it displaces and compresses the normal structures. Pagel's recent studies on the primary pulmonary focus in guinea pigs do not present any data on the early phase of the process.

The discussion has been limited intentionally to the primary focus in the lung tissue, because it is numerically the most important one in human pathology, and because of its elastic structure the lung offers better opportunities to differentiate infiltrating exudative and expansive productive lesions. On the strength of these studies, viewing the early lesion and considering the structure of the *centre* of the encapsulated focus, the conclusion must be drawn that the first response of pulmonary tissue to inhalation infection is an exudative-pneumonic lesion. It should be emphasized at the same time that this early reaction may very soon be followed by productive processes.

The concept that the primary response to the tubercle bacillus is a productive inflammation is based, to a large extent, on Baumgarten's studies on corneal infection. As excellent a ground for histogenetic studies the cornea may be, as unfair would it be to attempt a decision of the present question on its terrain. Since the cornea has no blood-vessels, an exudative reaction can never occur immediately following an injury, but only after vessels have been formed.

Krause, who stresses particularly the belief that the response of virgin tissue to the tubercle bacillus is productive, follows Baumgarten's concept and his own observations on extrapulmonary infections. It will be discussed later that the localization of bacilli plays an important rôle in determining the type of lesion. It is of particular interest, however, in this connection, to quote Krause verbatim:

Although we have examined scores of slides of recently infected lymph nodes we have never once seen a lesion begin and proceed in the manner that is considered characteristic of tuberculous infection; that is, as a more or less orderly and layered aggregation (proliferation) of cells. Nothing comes to view early that suggests the nodular nature of tubercle. These *early* changes in lymph nodes have no proliferative features about them; nor have they any inflammatory features, for accumulations of leucocytes are lacking. In the uniformly dark blue background (uniform except for the lighter germinal centres) that is made up mainly of lymphoid cells, one first notices extremely minute and angular lighter areas that look like little holes in the section. If then one turns a lens of higher power to these points, it is here that tubercle bacilli are most likely to be found. The areas appear light because the lymphocytes have disappeared from them, or, as in figure 4, because these are apparently necrotic and have become mere shadows. The periphery of these areas is not darker than usual; as has been said, there are no features of exudation (inflammation). As time goes on these areas become larger and larger, when they may stain uniformly yellow and now disclose that they are apparently made up of large cells that look like epithelioid cells: yet these are not arranged concentrically and in globular fashion as is the case in early tubercle in other tissues, and I have sometimes been of the opinion that they probably represent the normal reticulum cells of the node, which have been made more prominent because the lymphocytes are no longer present. As time goes on these cells may lose their nuclei as they become necrotic, in which event we are likely to see exudation for the first time, as the field becomes blackened with polymorphonuclear leucocytes and the necrotic tissue shows evidences of fragmentation.

Two points in this description are of eminent interest: first, the absence of productive changes, "the entire absence of *tubercle* (using the term in its histoanatomic sense)" and second, the statement that exudation is identified with accumulation of leucocytes. This latter statement, compared with the concept of the nature of tuberculous exudative processes as represented above, reveals another point where mere terminological differences lead to apparently material divergences. It is not at all unlikely that if proper agreement on the term *exudative* could be reached, unanimity would exist in regard to the histological nature of the primary infection. The fact that French and American observers of competence come to diametrically opposite interpretations of practically identical pictures shows the consequential fallacies of using terms whose significance is not agreed upon.

III. REINFECTION

Regarding the tissue reaction to reinfections general agreement exists on the broad statement that essentially the same tissue reactions occur as in a primary infection, but that the sequence of events is much more rapid and violent. It has been well brought out by the research work of recent years that the amount and the virulence of the primary infection, the interval between the first and second infection, and the nature of the reinfection, each in its turn, influence the histological changes to such an extent as to create a practically infinite variety of detailed phenomena. Depending on the interval between reinfection and histological examination, the picture will be more impressive as to the amount of early exudation, or as to the rapidity,—compared with a first infection,—with which productive tubercles are formed. The validity of this statement may well be exemplified by intrapleural or intraperitoneal infection in experimental animals. One may approach the study of the phenomena with two questions in mind, namely: (1) Will more exudate be found in an allergic than in a nonallergic animal? Answer: yes. Conclusion: the reaction in reinfection is predominantly exudative. (2) When do pleural or peritoneal (productive) tubercles appear in allergic and in nonallergic animals? Answer: much sooner in allergic animals. Conclusion: the reaction in reinfection is predominantly productive.

This accentuation of both the exudative and productive feature in reinfection is, for instance, stressed by Krause and Peters in their work on cutaneous reinfection; which feature predominates is, according to them, dependent on the dosage of reinfecting bacilli. They point out that if the reinfecting dosage is not too large, the incipient exudative reactions disappear readily, and the difference between normal and immune animals manifests itself in the accelerated development of productive tubercles in the latter. Krause makes a very strong case for his concept that exudative tuberculosis and caseation result only from reinfection, that is, under allergic conditions. This statement is well supported by clinical and particularly by experimental evidence. As is pointed out, the metastases resulting from *an* infection occurring later than two weeks after the first implantation of bacilli must be considered as happening in allergic soil. The main observation which does not agree with Krause's concept is the purely exudative nature of the primary focus,—at least in human lungs. In experimental infection,

too, one can produce extensive caseation at the site of infection in less than ten days if massive amounts of bacilli are introduced.

For any given state of allergy the dosage of the reinfecting bacilli is the factor which determines whether this allergy means immunity or hypersusceptibility, prolongation of life, or shortening of life. This paradox can be read in all the experimental work on the subject from Römer to Krause, and quite clearly again in the recent work by Soper and Dworsky on meningeal reinfection. And since allergy and dosage of reinfection are terms of quantitative correlation, only one conclusion seems to be possible; namely, that allergy and immunity,—always coëxisting,—are not identical conditions, and that one is not a direct measure of the other. Allergy may shorten and it may lengthen life, but immunity can have only *one* meaning.

Exudation and production of nodular tubercles are the two events which appear regularly in the otherwise varied course. The dominant feature in the early phase is exudation; it commands the chief practical interest, because its fate determines the clinical course of the disease. It may go on to complete caseation, or it may very completely resorb. From a clinical point of view the inquiry into the histological reaction to a reinfection resolves itself into the question of whether the final result is an extensive caseation in whose midst a few productive tubercules would play but an insignificant rôle, or whether the acute inflammatory reaction recedes and leaves the field to a productive lesion, whose potential fate has an altogether different clinical significance. Since the allergic condition of the body brought about by a previous infection, according to animal experimentation, is the causative factor in emphasizing both the exudative reaction and the reaction with the accentuation on the productive processes, it is obvious that the question whether reinfection leads to an exudative or productive reaction is beside the point. Only one fact is definitely known on the strength of animal experimentation: a practically avirulent tubercle bacillus after intratracheal infection will produce a lesion which slowly undergoes quite complete resorption (Gardner). This knowledge, obviously, is not pertinent in explaining the natural occurrences in progressive disease, where we deal presumably with virulent microörganisms only.

Which data of human pathology may help in an analysis of the problem? One may ask under which condition do we most regularly find purely exudative lesions? The answer will differ if given by the pathologist or if given by the clinician. The former will state that in

infants, in whom the first infection developed immediately into progressive pulmonary disease, in patients with rapidly and uninterruptedly advancing phthisis, and in the frequent preagonal bronchogenic propagations into the lower lung fields in chronic phthisics, such purely exudative lesions are found. All these conditions would indicate that the exudative type is wont to develop, when an allergic state had no time to develop, or, probably more correctly, during the incipient stage of allergy, or when it broke down under the stress of the disease. The clinician observes the exudative lesion in a few additional conditions. He sees the rather rapidly clearing pulmonary infiltrations in childhood and adolescence, the benign exudative manifestations comprised of old under the term of scrofula; he observes the benign and quite acute exudations in pleuritis and peritonitis; in many cases he will find that the frequent "colds" of his pulmonary patients are in fact acute and temporary circumfocal infiltrations around old foci; in brief, he, who unlike the pathologist, can observe the dynamics of the disease, must be impressed by the double-faced significance of the exudative lesion, its benignity and its malignancy. These contrary potentialities of the exudative reaction—resorption, the most ideal way of healing, and extensive caseation, the most dangerous course of a tuberculosis,—has long been known both to the experimentalist and to the observing clinician. Fränkel and Troje already in 1893 observed clinically far-reaching resorptions of tuberculous infiltrations. But it is only in the recent years of methodical X-ray studies that this phase has received definite attention. In the German literature the passing and, therefore, benign infiltrations have received a surprising number of different names. Eliasberg was so much impressed by their benignity that he doubted their tuberculous origin and suggested for them the name *epituberculous infiltration. Infraklavikuläre Infiltrate* (Assmann), *Primärinfiltrationen* (Redeker), *zircumfokale Reaktionen* (Ranke), are names designed to fit similar phenomena; the underlying pathology of all is essentially the same. In this country Amberson has emphasized the clinical significance of resorption by means of convincing series of X-ray photographs; many others have followed since. Surely, it cannot be the aim to differentiate clinically, roentgenologically, anatomically and immunologically exudative and productive lesions; it must be the aim to recognize the set of conditions which causes the resorbing and the caseating lesion. Being still far removed from such an aim, one may search at least for a working hypothesis to guide further research. An

hypothesis which offers as explanation for the *two* events (which must be distinguished) *the identical cause* is not acceptable.

At this point the work of Ranke, which has met with a great deal of recognition in the European literature, and which has found hardly any attention in America, should be carefully considered. Most painstaking histological studies lead him to an hypothesis which may be summarized briefly as follows: In the spontaneous evolution of tuberculosis three stages must be differentiated. The first stage, whose anatomical manifestation is the primary complex,—parenchymatous and lymphoglandular lesion,—is characterized by a strictly localized focus, with lymphatic metastasis into the draining lymphatic district only, by growth by contact, by an acute exudative process which is soon followed by productive inflammation along its border, and by the absence of collateral inflammation. In the secondary stage, the stage of generalization, the body has acquired an allergic condition whose predominant feature is an exquisitely exudative reaction, explained as a hypersensitiveness against the bacillus, developed as a response to the primary infection. This exudative type of reaction is shown by the acute inflammatory alterations at the site of any metastasis, and by very pronounced circumfocal inflammation, which in the case of affected lymph nodes is the inception of a sclerosing periadenitis. During this period the propagation occurs by any mechanically possible route: lymphogenous, haematogenous, in preformed tubules (intracanalicular), and by direct expansion. A further characteristic of this period (or at least of its early part) is the fact that any new metastasis gives rise in its turn to the development of a rapidly caseating lesion in its regional lymph nodes. As time progresses, the hypersensitiveness decreases and immunity increases: the exudative reactions become less violent, and both lymphogenous and haematogenous metastases recede in frequency and importance, until finally, in the third stage, they cease practically entirely and the intracanalicular propagation and the growth by contact are the only modes of evolution. Even the regional lymph nodes are not,—or are only very slightly,—affected in this stage of phthisis, limited to one organ-system (*organbeschränkte Phthise*). It needs no comment that Ranke's hypothesis attempts to outline only the basic features and that almost unlimited variety is possible within its confines. The secondary stage may pass clinically unnoticed; it may lead to multiple bone, joint, lymph-node, skin and other metastases; it may end fatally by its most malignant form, generalized miliary tuberculosis. The significance of this hypoth-

esis is the fact that on its basis the protean forms of tuberculosis are conceived as manifestations within *one* lawfully connected chain of occurrences, that an evolutive order is established, in which the most divergent appearances are recognized as causally connected members in the *one* process: the interaction of bacillus and host depending on a predictable development in the response of the body to the invader. Behring's statement that pulmonary tuberculosis of the adult is only the last stanza in the song, whose beginning was sung to the infant in the cradle, has thus received a basis of logical clarity and completeness.

Heuristically this theory appears to hold great promise. It explains the phenomena of benign generalization: scrofula, multiple lymph-node, bone and joint involvements, the manifestations of hypersensitiveness such as "idiopathic" pleurisies, phlyctenulae, tuberculides, the relative exclusiveness of extrapulmonary and pulmonary disease, the great rarity of generalized miliary tuberculosis in advanced pulmonary disease. But more important probably is the suggestion that the interaction of *two* types of allergy, the anaphylactic allergy of the secondary state, and the relative immunity in the third stage, may help to explain the benignity and malignancy of the exudative lesion. It is quite clear that the benign and passing infiltration is a manifestation of the former, and that the malignant caseating exudation occurs at times when the relative immunity is low, or not developed as yet. In pathological and clinical work based on Ranke's concept, it has become evident that the sequence of first, second and third stage is frequently not materialized. The predominant features of the secondary period, acute exudative reactions and hypersensitiveness, are frequently seen during the tertiary phase. What Ranke considered the secondary stage must properly be understood as a well-characterized immunological state, whose occurrence is not necessarily limited to the interval between primary infection and tertiary phthisis. Probably the most important example of its occurrence is the so called infraclavicular infiltration. Assmann, who described this lesion first, was the first to see such a focus on the postmortem table; its histological picture is that of a tuberculous pneumonic patch with central caseation. The significance of this process has been properly recognized by clinical studies during the last five years: all the evidence points to the probability that the exudative, suddenly appearing, nonapical lesions represent the inception of progressive pulmonary tuberculosis; and that the chronic apical foci with insidious symptomatology are only in the minority of cases the

endogenous source of active disease. In this light, the exudative tissue reaction assumes particular interest.

The exaggerated tuberculin reaction, which is observed during the manifestations of the "secondary stage," lends much support to Ranke's concept. This reopens the question of the quantitative relation between tuberculin allergy and tuberculosis immunity. No one will question to-day their interdependence. But the fact that, during a period of lymphogenous and haematogenous propagation, the tuberculin allergy is much more violent than during a time when the lesions are more or less confined to one organ, when blood and lymph channels are practically closed as roads of dissemination, this fact suggests strongly that the quantitative relation between allergy and immunity cannot be of a simple arithmetical order. Animal experimentation is not likely to add much to the solution of this question, since the laboratory animal,—after experimental infection,—usually dies in Ranke's second stage. Anatomical infection, followed by a more or less abortive dissemination, by a period of clinical latency, and finally by "phthisis" of one organ-system,—this most common event in human tuberculosis, is not reproduced in animals. This fact may go a long way to explain the essentially different concepts held by human pathologists and by experimentalists.

There is a very significant point of contact between Ranke's histological studies on human material and Krause's experimental studies. The latter has shown that in the allergic animal the generalization of the infection from the first deposit is much slower than in the non-prepared animals; in other words, an important feature of tuberculo-immunity is the fact that reinfecting bacilli are—to a degree—fixed at the portal of entry. Opie's work tends to prove that this mechanism is operative in all immunological responses. According to Krause two mechanisms are effective in fixing bacilli, in limiting the expansion of the disease. One is the immunological process, referred to above. Its manifestation is definite and clear, its nature is as mysterious as that of all "immunological phenomena." The other is an anatomical condition. In the young human being and similarly in the guinea pig, the lymphoid tissue in the lungs is scant, the channels are wide open; with increasing age the lymphoid tissue increases in volume, the passage of the lymph stream is impeded. These facts have been brought out by Miller's anatomical studies. Since the lymph-system plays undoubtedly a significant part both as roads of conveyance for the virus and as barrier

to further spread, it is evident that conditions in the young are much more favorable in regard to the unhindered spread of the disease throughout the body and that in the adult the tendency to localization is much more pronounced. The interaction of these two defensive mechanisms, one specific and acquired by a tuberculous infection, the other nonspecific and developed with increasing age, explains, according to Krause, the behavior of the mortality rate of tuberculosis in the various age-groups. In earliest childhood, with a high peak of mortality, neither allergic nor lymphatic defense is established. Then follows a very marked decrease in the mortality, due to the effects of the allergic defense. The allergy decreases as time goes on, unless subsequent infections keep it on a high level. There follows another peak in the mortality rate during adolescence, explained as a result of the decline in the specific resistance at a time when the lymphatic defense is not yet matured. The subsequent decline in the death-rate is a consequence of the fuller establishment of the lymphatic defense.

In comparing Ranke's and Krause's concepts, the question may be raised, whether the lymphatic development is, as stated by Krause, a purely nonspecific alteration caused probably by the unavoidable slight injuries of normal life, or whether it might not be a part of the specific tuberculous resistance. Anatomical studies on the lymphoid tissue in lungs of adults who have never been infected with tuberculosis are lacking. And, on the other hand, it is well known from studies on tuberculous patients belonging to so called nontuberculized races, that adults may react in essentially the same way to a primary infection as do children. This point is particularly stressed in Ranke's studies on the primary complex in adults. It seems of significance that both in Krause's and in Ranke's system essentially *two* modifying factors enter-in the first allergic and lymphatic defense, in the second hypersensitiveness and immunity are supposed to be in interplay.

Immunity, understood as a determining condition during the evolution of tuberculous disease, can have only *one* acceptable meaning: it is a condition which, *similia similibus,* tends to influence the course of the disease toward healing or toward benignity. At the present time we know essentially two types of healing processes: resorption, the dominant feature in exudative lesions; and fibrosis, the dominant feature in productive lesions. Most of the experimental work in recent years shows clearly the attempt to assign one type of tissue reaction to the allergic, the other type to the nonallergic condition. This desire for a histologico-

immunological correlation appears to have implied a neglect of the ultimate fate of the lesion. It is quite obvious that the exudative lesion is not malignant (corresponding to a low state of immunity) *eo ipso*, but only when it goes on to caseation, and similarly the productive lesion is not benign (corresponding to a high state of immunity) *eo ipso*, but only when it fibroses successfully. From a practical point of view we would have to ask, under what set of conditions does a lesion, productive or exudative, *heal* or *progress*, and not, as was mostly the case in experimental work, under what set of conditions does an exudative or productive lesion develop. From a practical point of view the dichotomy is not productive and exudative, corresponding in some way or other to allergic and nonallergic, but healing lesion and progressing lesion. Immunologically then, the dividing line is not to be drawn between exudative and productive reactions, but between healing (exudative or productive) lesions and progressive (exudative or productive) lesions. The following schema will represent the suggestion: the vertical line is the dividing line as usually applied, the horizontal line is the dividing line as set forth in the text:

exudative resorbing lesion	productive fibrosing (encapsulating) lesion
exudative caseating (and excavating) lesion	productive caseating (and excavating) lesion

The problem is further complicated by the fact, as pointed out above, that, at least in human pathology, we have no reliable way of measuring immunity. The quantitative relation between tuberculin allergy and true immunity can only be elucidated by carefully controlled tuberculin reactions in a large number of patients with healing (resorbing or fibrosing) lesions and with progressing lesions. The experimental work of Krause concerning this question outshines in completeness and accuracy the rather timid and scattered attempts in human pathology.

IV. MILIARY TUBERCULOSIS

The allergic condition cannot have exclusive importance in determining the cause of a lesion. Important as it is undoubtedly, other factors

must be considered. This is well exemplified by the fact that in the same body exudative and productive lesions may develop simultaneously, for instance, a basal bronchopneumonia and productive miliary tubercles in liver and spleen, which are both, undoubtedly, phenomena of the very last stage of the disease. Observations of this order are very numerous and known to every pathologist. One may assume that different organs are simultaneously in a different stage of allergy; and many observations on tuberculin tests would strongly suggest such a possibility; or the organ susceptibility may be influenced by local biochemical factors, as pointed out by Corper's experimental work. Another possibility has quite recently been emphasized again by Rolland and Hautefeuille, namely, that the number of bacilli deposited determines the type of lesion. Since the number of bacilli in a relatively immune organism (that is, a previously infected one) must be evaluated in its relation to the degree of immunity; this last possibility comes properly to discussion under the immunological behavior. Bezançon and Braun formulate a distinctly different opinion, which one may find by inference in Letulle's writings: namely, that the productive lesion is the response of the interstitial pulmonic tissue to the deposition of tubercle bacilli, while the respiratory parenchyma responds with the formation of exudative lesions to the same stimulus. According to their experiments in rabbits, the intravenous inoculation of bacilli produces productive interstitial tubercles, whereas intratracheal injection leads to the formation of miliary foci of pneumonic type. They point out that the apparently young "tubercles" found so frequently at autopsies in the lower lobes are usually miliary pneumonias and not productive tubercles; this fact, according to these views, is due to their bronchogenic origin.

In discussing the question of localization in miliary tuberculosis, reference must be made to Miller's studies which indicate that the physiological accumulation of lymphoid tissue is the favorite site for the deposition of bacilli. This most significant work is not further reported here because it does not bear any direct relation to the main point of this discussion. In this connection mention may be made of observations which seem to indicate that the portal of entry may materially modify the course of infection. Beitzke stated repeatedly that lymphoid tissue, a physiological organ of defense, will more successfully impede the propagation of bacilli, and with less severe histological reactions, than can the pulmonary parenchyma.

Korteweg and Loeffler pointed out that true miliary tuberculosis (according to definition) can occur only in allergic organisms. Intravenous inoculation of tubercle bacilli in a not previously infected animal produces multiple primary foci, which are histologically different from miliary tubercles. Korteweg, in studies on miliary tuberculosis in human beings, emphasized the observation that more or less all tubercles found in one case have the same characteristics as to size, density of seeding, number of bacilli, extent and progress of caseation, size of lymphocytic zone, and particularly of the amount of fibrotic reaction in the marginal areas. The same similarity exists in regard to the histological structure of the lesion; they tend either more to the type of productive tubercles, or to the type of miliary pneumonias. Grouping his cases in regard to histological criteria, Korteweg established a continuous chain from practically nonimmune conditions to conditions of highly developed immunity, the latter comprising the cases of the productive type with a well-marked fibrous margin. The uniformity of the lesions throughout one body suggested very strongly the idea that a general condition of the body, that is, allergy, may be the determining factor. Huebschmann and Arnold, too, point out that only a minority of "tubercles" in generalized miliary tuberculosis are of the classic type of cellular tubercles. They distinguish three types: (1) the miliary caseous pneumonia, which is found in cases with a rapid clinical course, and with leukopoenia; (2) typical productive forms with central caseation, giant cells, and of a more protracted clinical course with a slight leukopoenia, or with leukocytosis; and (3) border-line cases. The first acute type is found (in full agreement with Korteweg's observation) in cases whose miliary dissemination follows immediately the period of the primary complex or in patients with completely healed tuberculosis. The second type is observed more frequently with a coexisting tertiary phthisis (in Ranke's terminology). Huebschmann, too, emphasizes the significance of the allergic condition as the determinining factor. Meyenburg confirmed recently the essential parts of Huebschmann's observation. It must be granted that miliary tuberculosis can only occur in a previously infected, that is, allergic organism; that it is of haematogenous spread is beyond doubt. The observations just reported would, then, show at once, that neither allergy, simple and unqualified, nor the localization of the bacilli can each in itself be a sufficient criterion for the prediction of the type of lesions.

CONCLUSIONS

It is not in the nature of this analysis to arrive at "conclusions." However, a few points, it appears, are clearly brought out.

1. First, the necessity of a terminological understanding is paramount.
2. In human pathology, at least, the relation of allergy to immunity is obscure.
3. The allergic condition of the host cannot satisfactorily explain the occurrence of productive and of exudative lesions at the site of reinfection or metastasis.
4. Productive and exudative lesions, immunologically speaking, are not necessarily antagonistic; either may heal, and either may progress.
5. The immunological conditions under which healing or progression occurs are not well understood.
6. Important, although not exclusive, factors which determine the productive or exudative development of a lesion, are hypersensitiveness and resistance to bacilli, and localization and dosage of bacilli; a number of secondary factors must be considered.

A NOTE ON EXUDATIVE AND PRODUCTIVE PROCESSES IN PLEURAL TUBERCULOUS INFECTION[1,2]

MAX PINNER

In my paper, *Modern Concepts in the Pathology of Tuberculosis* (1), it was pointed out that the histological reaction to reinfecting tubercle bacilli has been variously interpreted as being predominantly exudative and as being predominantly productive in character. Considering the evidence based on clinical observation, a definite decision cannot be reached. Since, however, broad theories have been formulated in regard to the tissue reaction in reinfection, any evidence that might shed some light on this question appears deserving of mention. A full discussion of the problem would have to include at least the following points: (1) the relation of the degree of allergy to the type of tissue reaction; (2) the relation of the length of the time-interval between infection and reinfection to the histological reaction; (3) the relation of the dosage and virulence of reinfecting bacilli to the tissue reaction; and (4) the rôle which the site of reinfection plays.

But preceding all this, the question must be raised again whether the allergic tissue reaction is necessarily either of the productive or of the exudative type, since no agreement has been reached in regard to this point. Reinfection of a serous cavity would allow us to differentiate the two types of reaction most easily.

METHOD

Several series of rabbits, more than 60 in all, received intrapleural inoculations of measured amounts of living bovine tubercle bacilli of low virulence. More than half of these animals had been made allergic to tuberculin. This was achieved by various methods: some animals received several intraperitoneal injections of 25 or 50 mgm. of heat-killed bovine tubercle bacilli; others were infected subcutaneously with virulent

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] Part of this work was done in the Laboratory of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

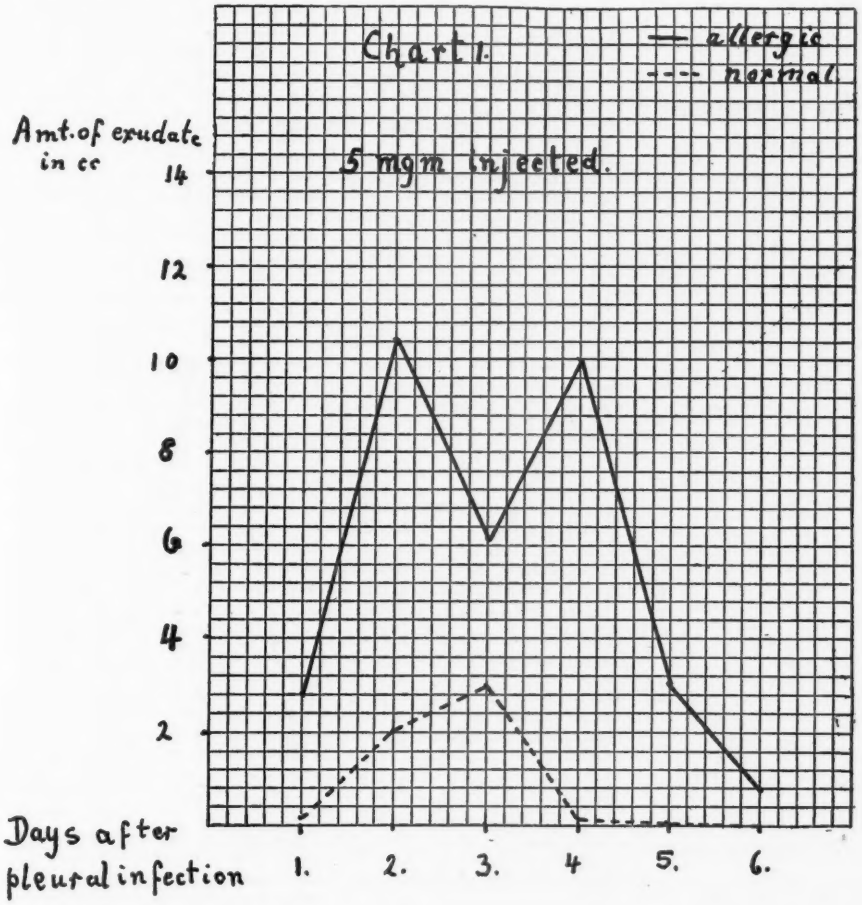
bovine or human bacilli. The respective series are much too small to make possible a comparison of the efficiency of the various methods in producing a strong tuberculin sensitiveness. All allergic animals used in these experiments were tested by intracutaneous tuberculin injections (0.1 cc. of a 1:5 solution of Old Tuberculin) a few days preceding the reinfection. Only such animals were used which developed a reaction of infiltration and hyperaemia, measuring not less than 1.5 cm. in diameter. For reinfection, always the same strain of low-virulent bovine bacilli was used. The dosage of reinfection in the various series was 0.1, 1.0, 2, 5, 10 and 20 mgm., respectively, of moist bacilli in a volume of 2 cc. saline solution. Previous to infecting the right pleural cavity, artificial pneumothorax with a slightly positive pressure (around 1 cm. of water) was established, either immediately before the inoculation, or a few days earlier. In no case was a communication between right and left pleural cavity observed.

The animals were killed at various intervals following the pleural infection. Whatever exudate was found in the right pleural cavity was removed with a capillary pipette and measured. The pleural surface of the right lung was carefully examined for tubercles and several pieces of lung tissue were sectioned and stained.

RESULTS

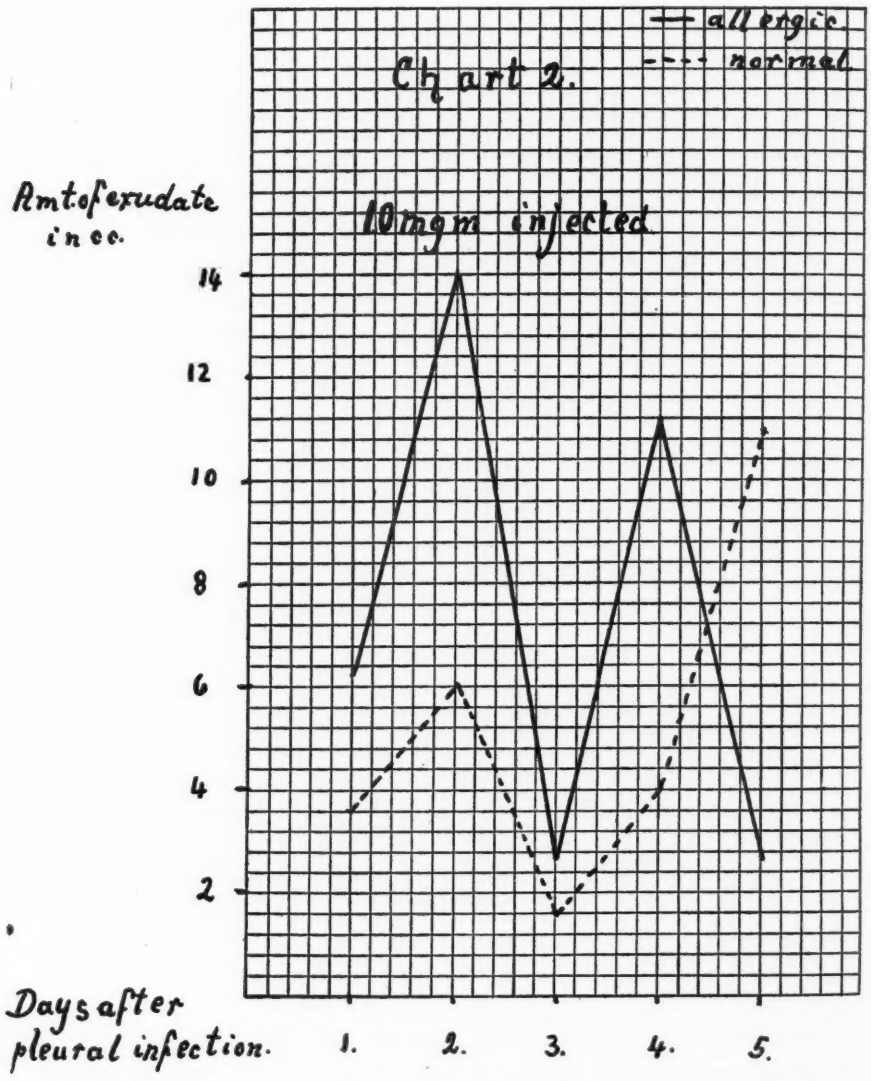
The exudative factor of the reinfection reaction was measured by the amount of pleural exudate. The appearance of pleural tubercles served as an indication for the productive factor. The term *tubercle* is used here strictly in its histopathological sense, meaning an accumultion of typical epithelioid cells in definite nodular arrangements, with or without giant cells. Young giant cells with three or four nuclei appeared in the very youngest formation; and it can be definitely stated that their appearance preceded rather regularly the slightest indication of caseation. The exudates were generally of a fibrinocellular nature and slightly sanguinolent. They always contained tubercle bacilli, many of which were phagocytosed in large mononuclear cells. If they could not be demonstrated readily in microscopic smears, some of the pleural fluid was incubated. After ten to fifteen days, as a rule, tubercle bacilli could easily be demonstrated microscopically. Part of the mononuclear cells could be identified as desquamated pleural endothelial cells, since they were frequently found in nondetached arrangements of 5 to 10 in exactly the same way as

found in scrapings of normal pleura. Some of these cells were highly active phagocytes; cells were seen which contained several tubercle bacilli, a red cell, and one or two polymorphonuclear leucocytes. There is little doubt, however, that not all the mononuclear cells were lining pleural cells.



For the question under discussion here, only two sets of data need be reported: namely, the amount of exudate and the time of appearance of typical tubercles. It is not intended to make any comparison between series of animals made allergic by different methods, nor of series of animals reinfected with different amounts of bacilli; the results in this regard are not conclusive, owing to an insufficient number of animals in

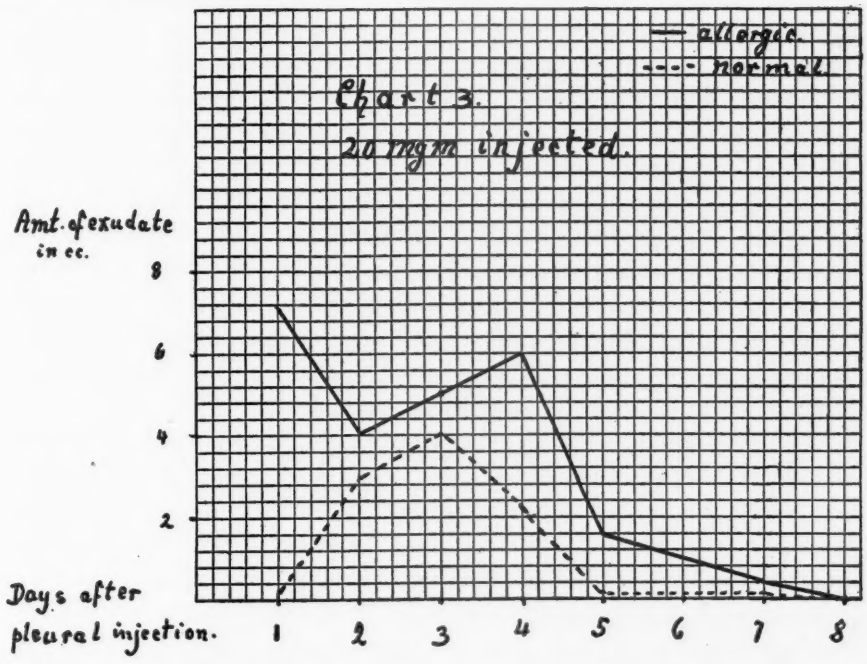
each set. The comparison presented here applies only to the two large groups of animals, namely, normal and allergic rabbits.



In neither group were exudates obtained when less than 5 mgm. of bacilli were injected. Charts 1 to 3 show the amounts of exudate developed following pleural infection. Composite curves are presented,

showing the average amount of fluid in two or three animals in each instance.

The earliest appearance of pleural tubercles in normal rabbits was eleven days after infection. In the allergic animals tubercles appeared as early as three days after infection. This was not the case in each animal, but after four or five days tubercles could always be demonstrated in the allergic rabbits. Not every nodule which looked macroscopically like a tubercle presented the typical microscopic picture. Quite frequently grayish-white, tiny nodules were observed on the pleural surface, espe-



cially upon the diaphragm, which were a dense, nodular agglomeration of lymphocytes with a few polymorphonuclear leucocytes. They were frequently more or less encapsulated by thin fibrin fibres, and resembled the lymphoid tubercles seen in the meninges in tuberculous meningitis. These formations are not included in the term *tubercles* as used here.

DISCUSSION

The outstanding finding in the experiments reported is the fact that the reinfection reaction as compared to primary infection is characterized by

increased exudation and by *accelerated production*. If attention is directed to only one of the two phases, the impression may be gained that reinfection is characterized either by exudation alone, or by production alone. Concepts of this type have greatly beclouded a proper understanding of the allergic tissue reaction. Paterson (2) in his studies on pleural reinfection in guinea pigs recorded only the exudative factor. Under his experimental conditions only the allergic animals developed exudates. This observation led him to the belief that a qualitative difference existed between the infection and reinfection reactions. He did not mention anything in his paper about the development of pleural tubercles. Corper and Rensch (3) attempted to duplicate Paterson's experiments on rabbits. They injected about 3 mgm. of human bacilli intrapleurally, and killed the animals four and eight days, and two, three and four weeks after the pleural injection. They noticed that both allergic and normal rabbits developed some fluid, and concluded that both groups of animals behaved in the same way in the response to pleural infection. Petroff and Stewart (4) again corroborated essentially Paterson's observation. It would appear that, according to the present experiments, the truth lies somewhere between the two statements mentioned. It is, of course, not possible to compare quantitatively the work of different authors, since conditions of allergy, strain peculiarities, individual and species differences in animals, cannot be sufficiently controlled.

Materially similar findings as presented here were recorded by Krause and Peters (5) on cutaneous reinfection and by Dworsky, Smith and Gardner (6) on intraperitoneal infection. The latter route of infection is evidently quite comparable to pleural infection. The latter authors reported the exaggeration of exudation and the acceleration of the appearance of "typical laminated tubercle" in allergic animals.

It should not be overlooked that the nonallergic animals, both in intraperitoneal and intrapleural infection, react with some definite amount of exudation. The allergic reaction, then, has no qualitatively distinguishing character, and there is no justification in assigning either the productive or the exudative type of tissue alteration to the state of allergy or anergy. The question of practical interest remains: namely, the final fate of the lesion. The conditions determining the ultimate outcome need much further study. In the pursuit of such work, it will be important not to pay attention exclusively to *one* phenomenon in the dual tissue alteration. Each *individual lesion* is either productive or exudative, but *the disease tuberculosis* which, at least in the human, involves always factors of allergy, presents an intimate and intricate mixture of both processes.

SUMMARY

In rabbits, made allergic to tuberculin by previous injections of living or heat-killed tubercle bacilli, the response to intrapleural infection by living bovine bacilli is characterized by an exaggeration of the exudative reaction and by an acceleration of productive processes, as compared with normal rabbits. Neither the nonallergic nor the allergic tissue reaction is purely productive or purely exudative.

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RECORDED AND RESIDENT DEATH-RATES FROM TUBERCULOSIS IN NEW YORK STATE IN 1926

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The generally accepted measure of the risk of death in a given period of time and in a given place is the fraction obtained by dividing the number of deaths in that place during the stated time by the number of people residing there. Thus, if we say that the death-rate in the State of New York in 1926 was 13.4 per 1,000 population, we mean that the risk of the "average" person dying in New York in 1926 was as 13.4 is to 1,000, or about one in seventy-five. If we were to define our "average" person within certain ages or limit him to one racial group or occupation, the risk of death would be expressed by relating the number of deaths occurring in the group to which our "average" person is now confined to the number of persons in that smaller population. In addition to the crude death-rates, based on mortality from all causes in the entire population, we have, therefore, specific death-rates by sex, age, cause of death, occupation, etc.

The rate of mortality would be a precise measure of the risk of death provided the numbers upon which it is based were exact, but we all recognize the inevitability of errors in the computation of a death-rate. There is, to begin with, the denominator of our fraction, namely, the estimated population, the accuracy of which is directly dependent upon its size and the interval of time separating the period considered from the last population count. On the other hand, even with a perfectly functioning system of registration, the total number of deaths ascribed to a certain cause does not necessarily represent the true mortality from this cause. Among the various reasons for this discrepancy, the accuracy of diagnosis is a consideration of some importance.

For the last few years statisticians and public-health workers have been endeavoring to determine whether or not the increase in the rates of mortality from certain diseases corresponds to a natural phenomenon or represents merely better medical diagnosis. The rather widespread

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suspicion on the part of the practitioner of the value of statistics has its basis in his recollection of the instances in which the judgment entered by him on a death certificate was, at best, a guess. He is, therefore, amused at times by the solemn manner in which statisticians often employ the imperfect material contained in death certificates as if it were the outcome of a rigorous process.

Another factor is found in the fact that a disease may be contracted in one place and the death occur in another place. If a group of city folks spend a day in the country and fill their organisms with typhoid germs from a rural stream the mortality among them certainly does not represent a true measure of the risk of death from typhoid in the city in which they permanently reside.

Among the several important causes of death, the element of residence is perhaps of greatest weight in mortality from tuberculosis. Here the traditional prescription of change of air is still operative and, in addition, there is the increasing number of hospitals and sanatoria with patients from diverse localities. The recorded death-rates from tuberculosis are for this reason, if for no other, not at all representative of the actual conditions in many urban and rural districts.[2] In the sixty-two counties of the State of New York, for example, the death-rates from tuberculosis, all forms, ranged in 1926 from 14.8 to 500.1 per 100,000 population, the rate for the entire State being 89.0. A variation of such a magnitude cannot be explained altogether by differences in occupation, greater or lesser salubrity of climate, age, sex, nativity of the population; it is clearly influenced by some extraneous factor which is evidently the matter of residence. The county with the highest death-rate is Franklin which contains several nationally and internationally known resorts for tuberculosis patients; most of the deaths recorded in this county were among nonresidents. Similarly, the published tuberculosis death-rates of many other sections of the State are fallacious.

To find a more accurate measure of mortality from tuberculosis, it is, therefore, necessary to ascertain the place in which the persons who died from the disease contracted it. Such an allocation of all deaths which were ascribed to tuberculosis in the State of New York in 1926 was made by the Division of Vital Statistics of the State Department of Health. It was not our purpose to undertake the difficult, if not impossible, task of uncovering all concomitant factors of high and low mortality. We

[2] The chance of an erroneous diagnosis in a fatal case of tuberculosis is nowadays rather small and does not affect seriously the recorded death-rate.

set ourselves the limited but concrete problem of merely finding a more accurate numerical measure of the loss of life from tuberculosis in the cities and counties of the State in the course of *one* year.

METHOD OF ALLOCATION

Deaths from tuberculosis, all forms, in the entire State in 1926 numbered 10,076; of these, 5,503 occurred in New York City and 4,573 in the rest of State.[3] The major portion of our analysis is limited to the upstate territory because the records of New York City are in the custody of the Department of Health of the City of New York. In order to determine the place to which each death should be charged the certificates were carefully examined for the last permanent residence of the decedents, the length of residence in the place where the death occurred and the duration of the illness. In all cases in which this information was not shown on the certificate, requests for it were sent to the local registrars. Statistically, the problem was not very complicated. If the place where the disease was contracted was stated on the certificate the death was charged to that place. When this information was not obtainable we compared the length of residence in the place where the death occurred with the duration of the illness: if the duration of the illness exceeded the length of residence, we assumed that the disease was contracted in the place in which the person previously resided; conversely, if the length of residence exceeded the duration of the illness, the disease was presumably contracted in the place where the death occurred. We realized the possibility of error on the part of the physician in specifying the duration of the illness and also the difficulty, with the best of intentions, of always being able to determine how long the patient had had tuberculosis. This is, however, a debatable question, even among members of the profession, and it is beyond the scope of a layman's discussion to decide whether tuberculosis is "contracted" or merely "developed." Here one is obliged to take the physician's statement upon its face value.

The certificates were examined by two experienced clerks, separately, and their conclusions agreed in about 96 per cent of the cases. The disposal of the doubtful remainder is described in detail later.

[3] The necessary data for New York City were obtained through the courtesy of Dr. William H. Guilfoy, Registrar of Records of the Department of Health of the City of New York.

The results obtained in the first general analysis follow:

	NEW YORK STATE (EXCLUSIVE OF NEW YORK CITY)	URBAN	RURAL	INSTITUTIONAL DISTRICTS
Total recorded deaths	4,573	2,342	1,765	466
Residents of place where death occurred	3,563	1,835	834	28
Nonresidents, place of residence known	601	287	754	426
Probable residents of place where death occurred	53	31	21	1
Probable nonresidents of place where death occurred	19	11	8	
Nonresidents whose residence was unknown or not stated	119	49	64	6
Residents of other states	200	120	75	5
Residents of foreign countries	18	9	9	

The difficulties encountered in the procedure of allocation may be grouped under three heads:

1: Incomplete or Inconsistent Data: Among the deaths in the entire area of the State, exclusive of New York City, in 191, out of 4,573 cases, the information shown on the death certificate was not sufficient for a definite judgment. In 53 of these cases the decedents were "probably" residents of the place where the death occurred, in 19 cases they were "probably" nonresidents, and in 119 cases they were definitely nonresidents, but the previous permanent place of residence was not established. Thus, about 96 per cent of the deaths could be allocated definitely on the basis of information shown on the certificates.

In computing the rates of the urban and rural parts of the State on the basis of residence we have excluded from the totals only those nonresidents whose place of residence was definitely known and have included in the totals all nonresidents whose permanent residence was unknown and also all persons who were "probable" residents and "probable" nonresidents. In doing it we were guided by the following consideration: In the urban part of the State the 49 persons who were nonresidents of the place in which death occurred, but whose residence was unknown, were residents of either some urban or rural communities. Similarly, the 64 persons in the same category in the rural part of the State were residents of either rural or urban communities. To allocate them in accordance with some theoretical ratio would introduce only

a semblance of accuracy, since one guess in this case would be as good as another. We have, therefore, counted the first group of 49 in the urban territory and the group of 64 in the rural territory, since, if the facts were known, the actual numbers undoubtedly would balance to a considerable extent.

In computing the totals of resident deaths and of resident death-rates in the cities and counties of the State we have included among them all "probable" residents and have excluded all "probable" nonresidents and those who were definitely nonresidents but whose place of residence was unknown. The deduction of the numbers under the last two groups results in numbers and rates from which, according to our best knowledge, all actual and possible nonresidents of the places are excluded. The rates are, therefore, in some cases somewhat lower than they would have been if the 138 deaths in which the information was insufficient could be allocated.

A few examples will illustrate the reasons for our inability to arrive at a decision in each case:

A Russian-Jewish woman, resident of Franklin County for three years, duration of illness shown as two years. Her previous place of residence, New York City; burial took place in New York City. While, on the surface, this should be classed as a resident death since the length of residence exceeded the duration of the illness, the other facts of the case make it appear doubtful and we have classed it as a "probable nonresident."

A native-born man, resident of Essex County for two years; duration of illness, one and one-half years; occupation, brakeman on Long Island Railroad; last residence, Brooklyn, N. Y. This was also classed under "probable nonresident."

A native-born woman, resident of Saranac Lake for two years; duration of illness, twelve months; previous residence and place where disease was contracted not stated: classed as a "probable resident."

In several instances the disease was said to have been contracted in "military service." These deaths were all entered as nonresidents, place of residence "unknown."

2: Deaths in Institutional Districts: The various State institutions and one large private institution (Our Lady of Victory Home, Lackawanna, N. Y.) were created in 1917 as separate registration districts. This was done because the majority of their inmates were nonresidents of the places in which the institutions were located. The State institutions

TABLE 1

New York State (exclusive of New York City): deaths from tuberculosis, all forms, in State institutions: 1926

INSTITUTION	POPULATION ON JANUARY 1, 1926	TOTAL RECORDED DEATHS	NONRESIDENT INMATES WHO CONTRACTED TUBERCULOSIS		RESIDENT INMATES*
			Prior to admission	After admission	
Total	51,645	466	108	318	40
Broome County:					
Binghamton Hospital	2,730	18	3	15	
Cayuga County:					
Auburn Prison	1,383				
Chemung County:					
Elmira Reformatory	1,235	1			1
Chenango County:					
Woman's Relief Corps Home	184				
Clinton County:					
Clinton Prison	571	5	2		3
Dannemora Hospital	1,427	1		1	
Columbia County:					
Training School for Girls, Hudson	404				
Dutchess County:					
Matteawan Hospital, Beacon	975	6	1	4	1
Hudson River Hospital, Poughkeepsie	3,858	62	13	47	2
Harlem Valley Hospital, Wingdale	269	2	1	1	
Erie County:					
Buffalo Hospital	2,190	15	4	9	2
Gowanda Hospital	1,268	10	1	8	1
Our Lady of Victory Infant Home and Hospital, Lackawanna†	225	4	4		
Essex County:					
Ray Brook Hospital for Incipient Tuberculosis	294	4	4		
Livingston County:					
Craig Colony for Epileptics, Sonyea	1,585	33	4	29	
Monroe County:					
Rochester Hospital	1,730	25		21	4
Oneida County:					
Rome Custodial Asylum	3,015	23	4	14	5
Utica Hospital	2,524	30	9	21	
Onondaga County:					
Institution for Feeble-Minded Children, Syracuse	854	3			3

* Including 5 residents of other States (Central Islip 2, Clinton Prison 1, Elmira Reformatory 1, Matteawan State Hospital 1), and 6 whose residence was unknown (Clinton Prison 1, Hudson River State Hospital 2, Kings Park State Hospital 2, Rochester State Hospital 1).

† Not a State institution, but constituted a separate district owing to its large nonresident inmate population.

TABLE 1—*Concluded*

INSTITUTION	POPULATION ON JANUARY 1, 1926	TOTAL RECORDED DEATHS	NONRESIDENT INMATES WHO CONTRACTED TUBERCULOSIS		RESIDENT INMATES*
			Prior to admission	After admission	
Orange County:					
Middletown Hospital	2,423	16	7	9	
Rockland County:					
Letchworth Village, Thiells	2,022	17	2	10	5
West Haverstraw Hospital	185	1	1		
St. Lawrence County:					
St. Lawrence Hospital	2,310	16	4	12	
Seneca County:					
Willard Hospital	2,502	37	14	21	2
Steuben County:					
Soldier's and Sailor's Home, Bath	272				
Suffolk County:					
Central Islip Hospital	5,704	69	17	50	2
Kings Park Hospital	4,993	61	13	42	6
Ulster County:					
Napanoch Reformatory	535	1			1
Washington County:					
Great Meadow Prison	931				
Wayne County:					
Newark Custodial Asylum	1,282	5		4	1
Westchester County:					
Sing Sing Prison	1,448	1			1
Bedford Reformatory for Women	317				

comprise State prisons, all State hospitals for insane, feeble-minded, delinquents, and the Ray Brook Hospital for Incipient Tuberculosis. In 1926 deaths from tuberculosis in these institutional districts numbered 466, or 10 per cent of the total recorded in the State, exclusive of New York City.

The facts regarding mortality in institutional districts by counties are summarized in table 1.

In 108 deaths recorded in institutional districts the physician who signed the certificate stated that the disease was contracted prior to the inmate's entrance into the institution; in 318 cases the disease was contracted in the institution; of the remaining 40 persons, 5 were residents of other states, 28 were stated to be permanent residents of the institution, and in 7 cases the information on the certificate was insufficient to

determine the status of the decedent. The distribution of the 108 cases in which it was definitely shown that the disease was contracted prior to the inmate's coming to the institution presented no difficulties: these deaths were allocated to the former place of residence. The 40 cases in which the decedents were stated to have been residents of the institution or of other States, or for which the information was incomplete, were left as a group under the rubric "Institutional Districts." The difficulty arose in determining upon the proper disposition of the 318 cases in which the disease was contracted in the institution, practically all in the State Hospitals for the Insane. Here it was possible to choose one of the following courses:

(1) Add this number to the 40 cases mentioned above and class them under the several institutions, and

(a) Include them with the totals shown for the counties in which the institutions are located, or

(b) Exclude them from the totals shown for the counties in which the institutions are located.

(2) Allocate these deaths according to the previous permanent place of residence of the decedent.

At first glance it would seem that there should be no cause for doubt in these 318 cases, since the certificates stated definitely that the disease was contracted in specified institutions. But the status of these persons, most of them mentally diseased, was not that of normal people moving to another place of residence, engaging in normal pursuits, living a normal life, and contracting tuberculosis. While these persons were in a physical sense residents of certain counties, the geographical location of an institution was of small consequence. Most of them would have developed tuberculosis whether the institution was located in one county or another. Here, conditions of segregated institutional life were the predominating factor, and this in turn was an outcome of the patient's mental breakdown. In other words, the first link in the chain of events was forged in the place in which the patient previously resided. We have, therefore, decided to treat these cases in a manner different from that applied to normal cases and to allocate them to their permanent place of residence prior to admission to a State institution.

There was another possible way of handling the problem and that was to charge these deaths against the institutions, but, in fairness to the counties in which the institutions are located, to eliminate them from the totals shown for these counties. Something may be said for the latter

solution, but for reasons stated above we gave it up in favor of the allocation.

Having allocated the institutional deaths it was also necessary to deduct the institutional populations from the populations of the several counties. There was no way by which we could compute the necessary population factor to account for the institutional deaths among former residents of the several counties, but the error introduced in failing to make the last correction was certainly less than the alternative of retaining the institutional population.

The institutional deaths did not increase materially the rates of the various cities and counties. A number of counties were not affected at all, while in the others the maximum number of deaths allocated from institutions was 18 in Westchester County, resulting in an increase of the rate from 63.1 to 67.2. Among the cities having a population of 10,000 or over the greatest number of additional deaths credited from institutions was 14 in Rochester, raising the resident rate from 73.3 to 77.7. In the majority of the other cities there was either none or one institutional death. On the other hand, the allocation of these deaths diminished considerably the rates of several counties harboring State institutions. In Dutchess County, for example, 50 institutional deaths which would otherwise be charged against the county were deducted, lowering the resident rate from 133.4 to 88.1. In Seneca County 21 institutional deaths were deducted, with a resulting reduction in the resident death-rate from 145.1 to 60.9. In Suffolk County 91 deaths were deducted, with a change in the resident rate from 109.5 to 49.6.

3. Residents of Foreign Countries and of Other States: The total of 4,573 deaths from tuberculosis, which occurred in the State, exclusive of New York City, in 1926 included 18 residents of foreign countries and 200 residents of other States. The residents of foreign countries were included among the residents of the State and of the various subdivisions in which their deaths were recorded. In the case of residents of other States the procedure adopted for residents of foreign countries seemed also most logical for the larger subdivisions of the State, since, not having any information regarding the deaths from tuberculosis in other States of residents of New York, there was certainly no reason for reducing the recorded mortality by the fairly large number of deaths of nonresidents of the State. Our totals for the rest of State and for its urban and rural areas include, therefore, in the column "Residents" the deaths of residents

of other States. In considering the individual counties and cities we had to follow a different path because the nonresidents of the State figured largely in only five counties, namely, Dutchess, Erie, Essex, Franklin, and Sullivan. In Franklin, for example, were recorded 60 deaths of residents of other States, more than one-quarter of all deaths from tuberculosis in that county. To include these deaths would result, clearly, in introducing a big error, since, if there were any deaths from tuberculosis in other States of residents of Franklin County, their number would certainly not balance the deaths of residents of other States within the limits of Franklin County. Similar considerations argued against the inclusion of residents of other States in the totals of the other four counties. We have, therefore, excluded residents of other States from the totals for all counties and have followed a similar procedure in computing the total of resident deaths in the rural areas of counties and in the cities of the State, except New York City, for which this information was not available.

The deaths of residents of other States, which occurred in the State of New York (exclusive of New York City), are listed as follows:

New Jersey	70	Maine	2
Pennsylvania	36	New Mexico	2
Massachusetts	14	South Carolina	2
Ohio	10	U. S. Territories	2
Maryland	8	Alabama	1
District of Columbia	7	Colorado	1
Michigan	7	Delaware	1
Vermont	7	Iowa	1
Connecticut	5	Minnesota	1
Illinois	4	Missouri	1
Virginia	4	New Hampshire	1
California	3	North Dakota	1
Florida	2	Rhode Island	1
Georgia	2	Tennessee	1
Indiana	2	West Virginia	1

MORTALITY FROM TUBERCULOSIS ACCORDING TO THE NATURE OF PLACE WHERE DEATH OCCURRED

We have tabulated the deaths from tuberculosis upstate in 1926 according to the nature of the place where they occurred. There is, to begin with, the largest class, which, for want of a better term, we have called "Private Dwellings;" all other places being arranged in twelve groups. The results are given in table 2.

Of the 4,573 deaths recorded in 1926 in the State, exclusive of New

York City, 54 per cent occurred in private dwellings and 46 per cent in institutions of various types. The numerically largest group of institutions represented in this analysis are tuberculosis hospitals and sanatoria

TABLE 2

New York State (exclusive of New York City): deaths from tuberculosis, all forms, by place of death: 1926

PLACE OF DEATH	NUMBER	PER CENT OF TOTAL
Total recorded deaths	4,573	100.0
Private dwellings	2,469	54.0
Institutions	2,104	46.0
Tuberculosis hospitals and sanatoria	1,276	27.9
County	670	14.7
Local	417	9.1
Federal	139	3.0
Private	46	1.0
State (Ray Brook)	4	0.1
Institutions for feeble-minded and insane	452	10.0
State hospitals for insane	361	7.9
State institutions for mental defectives	81	1.8
State hospital for criminal insane	7	0.2
Institutions for feeble-minded and insane (not State)	3	0.1
General, special, and surgical hospitals and sanatoria (not for tuberculosis)	268	5.8
Local and county	266	5.8
Federal	2	*
County and city homes and almshouses	75	1.6
Schools, convents, State and private schools, or colleges	9	0.2
State and private curative institutions (not for tuberculosis or for insane)	6	0.1
State prisons	6	0.1
Industrial homes, training schools and reformatories	4	0.1
State	2	*
Other	2	*
Maternity hospitals and infant homes	3	0.1
Fraternal and church homes	2	*
Hospitals for incurables	2	*
Homes for aged	1	*

* Less than one-tenth of one per cent.

with 1,276 deaths, or 27.9 per cent of the total. Among these, county hospitals held first place with 14.7 per cent; city or village hospitals, 9.1 per cent; federal hospitals, 3.0 per cent; private sanatoria, 1.0 per cent; and the one State Hospital for Incipient Tuberculosis at Ray Brook, 4 deaths or 0.1 per cent.

Deaths in institutions for feeble-minded and insane, practically all under State auspices, accounted for 452, or 10 per cent of all deaths. City and county hospitals, not for tuberculosis patients, recorded 262 deaths, or 5.7 per cent of the total. The remaining deaths occurred in numerous institutions of a type different from the ones mentioned above.

RECORDED AND RESIDENT DEATH-RATES OF MAIN DIVISIONS OF THE STATE

Table 3 summarizes the results of the allocation of deaths according to residence in the main subdivisions of the State. In New York City, in 1926, deaths from tuberculosis numbered 5,503; of these, 5,469 were residents of the City and 34 residents of the State, exclusive of New York City. But 601 residents of New York City died in the rest of State, making the total number of deaths from tuberculosis of residents of New York City, 6,070. The deaths of New York City residents which occurred upstate were recorded in the counties as follows:

County	*Deaths*	*County*	*Deaths*
Suffolk	122	Saratoga	3
Sullivan	106	Schenectady	3
Franklin	84	Delaware	2
Dutchess	80	Albany	1
Orange	36	Columbia	1
Essex	32	Herkimer	1
Westchester	22	Lewis	1
Livingston	19	Monroe	1
Seneca	14	Montgomery	1
Oneida	12	Onondaga	1
Ulster	10	Ontario	1
Rockland	9	Oswego	1
Broome	8	Otsego	1
Nassau	8	Putnam	1
Greene	7	Schoharie	1
Erie	4	Tioga	1
Clinton	3	Washington	1
St. Lawrence	3	*Total*	601

The recorded number of deaths from tuberculosis in the rest of State was 4,573. Of these, 3,972 were residents of that part of the State and 601 residents of New York City. Adding to the number of residents of the rest of State who died within that territory, 34 residents who died in New York City, we have a total of 4,006. The death-rates per 100,000 population, based on recorded deaths, were 92.9 in New York City and 84.8 in the rest of State; the rates computed on the basis of resident

deaths, irrespective of the place of their occurrence within the State, are 102.5 for New York City and 74.3 for the rest of State. Thus, the resident death-rate of New York City is 10 per cent higher and the resident death-rate of the rest of State 12 per cent lower than the recorded rates.

Deaths recorded in the urban[4] part of the State, exclusive of New York City, numbered 2,342. Of these, 2,055 were residents of that part of the State, 180 were residents of New York City, and 107 were residents of rural New York. To the number of deaths of residents of the urban territory must be added 23 deaths of residents which occurred in New York City, 542 in the rural part of the State, and 147 in institutional

TABLE 3

New York State: deaths from tuberculosis, all forms, by residence of decedent, and recorded and resident death-rates: 1926

PLACE OF DEATH	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS* OF					DEATH-RATES PER 100,000 POPULATION	
			New York City	Rest of State					
				Total	Urban	Rural	Institutional Districts	Recorded	Resident
New York State	11,318,734	10,076	6,070	4,006	2,767	1,199	40	89.0	89.0
New York City	5,924,018	5,503	5,469	34	23	11		92.9	102.5
Rest of State	5,394,716	4,573	601	3,972	2,744	1,188	40	84.8	74.3
Urban	3,326,331	2,342	180	2,162	2,055	107		70.4	83.2
Rural	2,017,177	1,765	212	1,553	542	1,011		87.5	59.4
Institutional districts	51,208	466	209	257	147	70	40		

* Includes residents of other States and foreign countries and those whose residence was unknown or not stated.

districts, making a total of 2,767 deaths. The recorded death-rate was 70.4, while the resident death-rate is 83.2.

Deaths recorded in the rural[4] part of the State numbered 1,765. Of these, only 1,011 were residents of that part of the State, 542 were residents of urban New York, and 212 residents of New York City. Rural residents who died in other parts of the State were as follows: 11 in New York City, 107 in urban New York, and 70 in institutional districts, the total of resident deaths being, therefore, 1,199. The recorded death-

[4] *Urban* includes cities and other incorporated places, whose population, at the State Enumeration of 1925, was 2,500 or more; *rural* includes the remainder of the State, exclusive of institutional districts.

rate of rural New York was 87.5, while the resident rate is 59.4. Allocating deaths according to residence increases the rate of the urban part of the State by 18 per cent and decreases the rural rate by 32 per cent. Thus, while the recorded death-rate in the rural part of the State was 24 per cent above the urban (exclusive of New York City), the relation between the resident rates is more than reversed and the urban exceeds the rural rate by 40 per cent.

The resident death-rate of the urban area remains higher than the rural rate even if all doubtful cases are charged to rural districts. Thus, assuming that in the urban communities the 31 "probable" residents, 11 "probable" nonresidents and 49 nonresidents, whose residence was unknown or not stated, were all residents of rural New York, we obtain a total of 2,676 deaths of persons, who were, so far as the information on the death certificates enables us to judge, certainly residents of the urban territory; the rate based on this number is 80.4. If, on the other hand, we retain in the rural area the 93 doubtful cases and add the 91 doubtful urban cases the total is increased to 1,290, and the rate becomes 64.0. The excess of the urban rate, with a bias designedly in its favor, is 26 per cent.

CONCISE DESCRIPTION OF MAIN TABLES AND MAPS

Tables 4, 5, and 6 show the recorded and resident death-rates of all cities and villages having a population of 10,000 and over, and of rural and total areas of the fifty-seven counties of the State, exclusive of New York City, together with the necessary intermediate steps leading to the computation of the resident death-rates. Column 2 gives the population of each place estimated as of July 1, 1926; column 3, the number of recorded deaths, in tables 4 and 5 exclusive of deaths in State institutions, in table 6 inclusive of these deaths. In table 6, column 4 shows the number of persons who were residents of the county in which the death occurred; column 5, those who were residents of other parts of the State, including, in the case of a few counties, residents of foreign countries; column 6 shows the number of residents of other States. Column 7 gives the deaths of residents of the county which occurred elsewhere in the State. Adding columns 4 and 7 we get column 8, giving the total number of deaths of residents. Column 9 gives the death-rates as recorded and column 10, resident death-rates.

The arrangement of tables 4 and 5 is identical with that of table 6,

TABLE 4

Urban area of New York State: deaths from tuberculosis, all forms, by residence of decedent, with recorded and resident death-rates, in places having a population of 10,000 or more: 1926

CITY OR VILLAGE	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS OF				RESIDENTS OF CITY OR VILLAGE DYING ELSEWHERE IN STATE	TOTAL DEATHS OF RESIDENTS	DEATH-RATES PER 100,000 POPULATION	
			City or Village	Rest of County	Other parts of State	Other States			Recorded	Resident
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
New York City	5,294,018	5,503	5,469		34	§	601	6,070	92.9	102.5
Buffalo*	542,060	512	424	47	26†	15	37	461	94.5	85.0
Rochester*	319,242	163	152	4	5	2	96	248	51.1	77.7
Places 100,000–250,000	524,790	374	309	23	36	6	130	439	71.3	83.7
Albany	118,715	142	104	13	23	2	27	131	119.6	110.3
Syracuse*	188,845	89	76	5	6	2	60	136	47.1	72.0
Utica*	100,889	54	47	3	3	1	27	74	53.5	73.3
Yonkers	116,341	89	81	2	5	1	17	98	76.5	84.2
Places 50,000–100,000	346,250	165	145	5	10	5	129	274	47.7	79.1
Binghamton*	70,185	25	23	1		1	30	53	35.6	75.5
Mount Vernon	51,913	20	17		1	2	17	34	38.5	65.5
Niagara Falls	58,288	29	28		1		23	51	49.8	87.5
Schenectady	93,599	28	19	2	6	1	26	45	29.9	48.1
Troy	72,265	63	58	2	2	1	33	91	87.2	125.9
Places 25,000–50,000	392,680	286	202	49	30	5	94	296	72.8	75.4
Amsterdam	35,607	25	23		2		11	34	70.2	95.5
Auburn*	34,286	27	19	2	6		5	24	78.7	70.0
Elmira*	47,622	20	16	1	2	1	10	26	42.0	54.6
Jamestown	44,313	23	20			3	14	34	51.9	76.7
Kingston	28,381	44	30	10	4		3	33	155.0	116.3
Newburgh	30,430	33	22	6	4	1	5	27	108.4	88.7
New Rochelle	45,824	11	11				10	21	24.0	45.8
Poughkeepsie	35,804	32	25	5	2		14	39	89.4	108.9
Rome*	28,560	31	8	21	2		4	12	108.5	42.0
Watertown	33,146	26	17	4	5		2	19	78.4	57.3
White Plains	28,707	14	11		3		16	27	48.8	94.1
Places 10,000–25,000	632,494	307	257	18	23	9	210	467	48.5	73.8
Batavia	16,045	11	8	3			2	10	68.6	62.3
Beacon*	10,757	9	8		1		5	13	83.7	120.9
Cohoes	23,417	7	7				9	16	29.9	68.3

* Exclusive of State institutions.

† Including 2 residents of foreign countries.

§ Not shown separately for New York City; included in column 4.

TABLE 4—*Concluded*

CITY OR VILLAGE	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS OF				RESIDENTS OF CITY OR VILLAGE DYING ELSEWHERE IN STATE	TOTAL DEATHS OF RESIDENTS	DEATH-RATES PER 100,000 POPULATION	
			City or village	Rest of County	Other parts of State	Other States			Recorded	Resident
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Corning	15,722	9	8		1		2	10	57.2	63.6
Cortland	13,996	3	2		1		2	4	27.4	28.6
Dunkirk	20,027	11	11				6	17	54.9	84.9
Endicott	16,192	3	3				4	7	18.5	43.2
Freeport	14,964	11	7		2	2	4	11	73.5	73.5
Fulton	12,571	6	6				3	9	47.7	71.6
Geneva	16,160	4	2		2		4	6	24.8	37.1
Glen Cove	11,254	2	2				3	5	17.8	44.4
Glens Falls	18,094	6	4		2		4	8	33.2	44.2
Gloversville	22,117	3	3				3	6	13.6	27.1
Hempstead	10,666	5	4		1		5	9	46.9	84.4
Herkimer	11,001	9	7		2		5	12	81.8	109.1
Hornell	15,936	7	5	1		1	2	7	43.9	43.9
Hudson*	11,353	13	11	1	1		6	17	114.5	149.7
Ilion	10,477	6	5	1			5	10	57.3	95.4
Ithaca	19,337	7	4	3			5	9	36.2	46.5
Johnson City	11,685	3	3				4	7	25.7	59.9
Johnstown	10,712	5	5				4	9	46.7	84.0
Lackawanna*	20,427	11	10		1		23	33	53.9	161.6
Little Falls	12,428	7	7				5	12	56.3	96.6
Lockport	21,750	3	3				7	10	13.8	46.0
Mamaroneck	10,869	5	5				4	9	46.0	82.8
Middletown*	18,329	20	13	2	2	3	2	15	109.1	81.8
North Tonawanda	17,731	12	9	1	2		8	17	67.7	95.9
Ogdensburg*	15,226	5	4	1			2	6	32.8	39.4
Olean	21,497	9	8			1	5	13	41.9	60.5
Oneida	10,679	3	3					3	28.1	28.1
Oneonta	12.152	6	6				1	7	49.4	57.6
Ossining*	11,684	6	5	1			5	10	51.4	85.6
Oswego	22,369	8	7		1		11	18	35.8	80.5
Peekskill	18,418	4	4				4	8	21.7	43.4
Plattsburg	11,681	16	11	4		1	1	12	137.0	102.7
Port Chester	19,825	13	10	2	1		8	18	65.6	90.8
Port Jervis	10,574	4	4				5	9	37.8	85.1
Rensselaer	11,508	2	2				8	10	17.4	86.9
Rockville Center	11,127	4	2		2		3	5	35.9	44.9
Saratoga Springs	14,025	13	10	1	1	1	9	19	92.7	135.5
Tonawanda	11,537	7	7				7	14	60.7	121.3
Watervliet	16,175	9	9				8	17	55.6	105.1
Places 2,500–10,000	568,815	535	210	13	234‡	78	183	393	94.1	69.1

‡ Including 7 residents of foreign countries.

TABLE 5

Rural area of New York State: deaths from tuberculosis, all forms, by residence of decedent, with recorded and resident death-rates: 1926

RURAL AREA OF COUNTY	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS OF—				RESIDENTS DYING ELSEWHERE IN STATE	TOTAL DEATHS OF RESIDENTS	DEATH-RATES PER 100,000 POPULATION	
			Rural part of County	Rest of County	Other parts of State†	Other States			Recorded	Resident
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Albany	36,508	20	15	2	2	1	6	21	54.8	57.5
Allegany	31,962	11	6	1	2	2	4	10	34.4	31.3
Broome*	38,535	45	9	28	5	3	4	13	116.8	33.7
Cattaraugus	40,868	49	15	8	26		1	16	119.9	39.2
Cayuga*	29,795	12	8	2	2		2	10	40.3	33.6
Chautauqua	49,591	34	14	17	1	2		14	68.6	28.2
Chemung	19,706	11		8	3		3	3	55.8	15.2
Chenango*	27,199	20	13	4	2	1	3	16	73.5	58.8
Clinton*	32,849	16	16				6	22	48.7	67.0
Columbia*	31,728	29	19	3	7		2	21	91.4	66.2
Cortland	14,748	4	4				1	5	27.1	33.9
Delaware	40,094	25	17	1	6	1	1	18	62.4	44.9
Dutchess*	45,410	139	23	16	76	24	4	27	306.1	59.5
Erie*	94,961	32	27	3	2		20	47	33.7	49.5
Essex*	25,893	28	14	1	10	3	4	18	108.1	69.5
Franklin	29,009	84	17	2	50	15	3	20	289.6	68.9
Fulton	13,268	9	1	5	3			1	67.8	7.5
Genesee	24,043	9	8		1		5	13	37.4	54.1
Greene	23,266	24	14		10		8	22	103.2	94.6
Hamilton	4,296	2	2				1	3	46.6	69.8
Herkimer	22,768	29	11	10	8		2	13	127.4	57.1
Jefferson	48,757	17	17				5	22	34.9	45.1
Lewis	21,428	6	5		1		1	6	28.0	28.0
Livingston*	29,955	9	6		3		5	11	30.0	36.7
Madison	26,114	12	11		1		2	13	46.0	49.8
Monroe*	64,770	102	25	73	3	1	9	34	157.5	52.5
Montgomery	18,074	26	12	13	1		3	15	143.9	83.0
Nassau	117,303	75	44	21	10		13	57	63.9	48.6
Niagara	31,868	41	8	30	2	1	3	11	128.7	34.5
Oneida*	56,604	24	20	2	1	1	13	33	42.4	58.3

* Exclusive of State institutions.

† Figures in this column include residents of foreign countries as follows: Albany, Greene, Herkimer, Rockland, Saratoga, Suffolk and Sullivan, 1 each; Franklin, 2.

TABLE 5—*Concluded*

RURAL AREA OF COUNTY	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS OF—				RESIDENTS DYING ELSEWHERE IN STATE	TOTAL DEATHS OF RESIDENTS	DEATH-RATES PER 100,000 POPULATION	
			Rural part of County	Rest of County	Other parts of State†	Other States			Recorded	Resident
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Onondaga*	66,320	67	16	44	7		8	24	101.0	36.2
Ontario	31,846	31	18	3	10		2	20	97.3	62.8
Orange*	54,553	59	28	1	29	1	9	37	108.2	67.8
Orleans	19,568	10	8		1	1	6	14	51.1	71.5
Oswego	36,882	38	22	11	5		4	26	103.0	70.5
Otsego	32,735	27	21	1	4	1	1	22	82.5	67.2
Putnam	12,840	9	7		2		5	12	70.1	93.5
Rensselaer	30,635	57	13	27	17		1	14	186.1	45.7
Rockland*	35,501	27	13	6	7	1	5	18	76.1	50.7
St. Lawrence*	57,737	20	16	2	2		6	22	34.6	38.1
Saratoga	31,071	45	20	7	13	5	1	21	144.8	67.6
Schenectady	18,776	34	10	17	6	1	1	11	181.1	58.6
Schoharie	18,997	8	7		1		5	12	42.1	63.2
Schuyler	10,582	2	2				1	3	18.9	28.4
Seneca*	12,557	10	8		2		1	9	79.6	71.7
Steuben*	46,837	28	16	1	10	1	3	19	59.8	40.6
Suffolk	108,547	61	43	4	13	1	10	53	56.2	48.8
Sullivan	34,631	77	20		50	7	2	22	222.3	63.5
Tioga	15,989	8	5		3		1	6	50.0	37.5
Tompkins	21,077	14	6	5	3		5	11	66.4	52.2
Ulster*	48,077	46	31	1	13	1	9	40	95.7	83.2
Warren	16,456	13	12		1		5	17	79.0	103.3
Washington*	26,799	15	12	1	2		4	16	56.0	59.7
Wayne*	35,342	13	12		1		3	15	36.8	42.4
Westchester*	66,117	92	26	54	12		8	34	139.1	51.4
Wyoming	22,949	9	8		1		1	9	39.2	39.2
Yates	12,386	1	1					1	8.1	8.1

with the exception of an additional column (5) which gives the deaths occurring in the rest of county, that is, in table 4 the county minus the indicated city or village, and in table 5 the county minus the rural part. The other columns correspond to those in table 6, their order increased by one.

TABLE 6

New York State (exclusive of New York City): deaths from tuberculosis, all forms, by residence of decedent, with recorded and resident death-rates, by counties: 1926

COUNTY	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS OF			RESIDENTS DYING ELSEWHERE IN STATE	TOTAL DEATHS OF RESIDENTS	DEATH-RATES PER 100,000 POPULATION	
			County*	Other parts of State†	Other States			Recorded	Resident
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Albany	199,345	179	151	24	4	38	189	89.8	94.8
Allegany	36,815	13	8	2	3	4	12	35.3	32.6
Broome	139,327	94	72	18	4	8	80	67.5	58.6
Cattaraugus	74,268	62	34	27	1	5	39	83.5	52.5
Cayuga	65,464	39	31	8		3	34	59.6	53.1
Chautauqua	130,650	74	66	3	5	8	74	56.6	56.6
Chemung	73,481	36	27	7	2	6	33	49.0	45.7
Chenango	35,743	22	19	2	1	6	25	61.6	70.3
Clinton	46,528	38	32	3	2	3	35	81.7	78.6
Columbia	43,485	42	34	8		4	38	96.6	88.2
Cortland	31,336	7	6	1		4	10	22.3	31.9
Delaware	43,605	26	19	6	1	1	20	59.6	45.9
Dutchess	100,447	251	81	145	25	3	84	249.9	88.1
Erie	705,395	598	539	41	15	34	573	84.8	81.7
Essex	32,096	103	23	58	22	2	25	320.9	78.6
Franklin	46,390	232	33	139	60	4	37	500.1	79.8
Fulton	46,292	17	14	3		2	16	36.7	34.6
Genesee	44,508	22	21	1		6	27	49.4	60.7
Greene	28,689	30	20	9	1	13	33	104.6	115.0
Hamilton	4,296	2	2			1	3	46.6	69.8
Herkimer	67,215	53	43	9	1	9	52	78.9	77.4
Jefferson	86,481	47	42	5		4	46	54.3	53.2
Lewis	24,915	9	8	1		2	10	36.1	40.1
Livingston	39,713	45	9	36		5	14	113.3	36.7
Madison	41,062	17	16	1		3	19	41.4	46.3
Monroe	400,217	296	276	14	3	18	294	74.0	73.8
Montgomery	62,076	54	51	3		5	56	87.0	90.2
Nassau	224,015	109	88	19	2	26	114	48.7	50.9
Niagara	136,384	85	79	5	1	13	92	62.3	67.5
Oneida	199,613	170	118	44	3	8	126	85.2	64.9

TABLE 6—*Concluded*

COUNTY	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS OF			RESIDENTS DYING ELSEWHERE IN STATE	TOTAL DEATHS OF RESIDENTS	DEATH-RATES PER 100,000 POPULATION	
			County*	Other parts of State†	Other States			Recorded	Resident
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Onondaga	272,124	165	146	14	2	22	168	60.6	61.9
Ontario	55,758	37	25	12		4	29	66.4	52.0
Orange	126,929	142	88	49	5	8	96	111.9	77.1
Orleans	31,108	16	13	2	1	8	21	51.4	67.5
Oswego	71,822	52	46	6		7	53	72.4	73.8
Otsego	47,644	35	29	5	1	2	31	73.5	65.1
Putnam	12,840	9	7	2		5	12	70.1	93.5
Rensselaer	119,489	126	106	19	1	16	122	105.4	102.1
Rockland	58,613	60	33	21	1	4	37	102.4	65.6
St. Lawrence	92,569	50	34	16		6	40	54.0	44.3
Saratoga	66,728	70	48	14	8	7	55	104.9	82.4
Schenectady	118,178	63	49	12	2	12	61	53.3	51.6
Schoharie	21,617	8	7	1		5	12	37.0	55.5
Schuyler	13,528	2	2			1	3	14.8	22.2
Seneca	25,497	48	11	35		3	14	188.3	60.9
Steuben	82,815	44	31	11	2	5	36	53.1	43.6
Suffolk	149,840	202	59	136	3	10	69	134.8	49.6
Sullivan	41,598	170	30	117	23	5	35	408.7	84.1
Tioga	26,491	10	6	3	1	5	11	37.7	41.5
Tompkins	40,414	21	18	3		2	20	52.0	49.5
Ulster	84,620	97	77	17	2	5	82	114.6	97.5
Warren	34,550	19	16	3		9	25	55.0	72.4
Washington	46,686	24	22	2		10	32	51.4	69.3
Wayne	52,485	28	22	5		6	28	53.3	54.7
Westchester	442,059	283	251	27	4	45	296	64.0	67.2
Wyoming	30,989	14	12	2		5	17	45.2	54.9
Yates	17,874	6	6			2	8	33.6	44.8

N. B. For counties having State institutions, the recorded deaths (column 3) and recorded death-rates (column 9) refer to the entire county including the State institutions. The resident death-rates (column 10) are based on resident deaths and the populations of the several counties, exclusive of the populations of the State institutions.

* Deaths of 40 inmates of State institutions were not allocated, (for details see table 1). These deaths were deducted from the totals of counties in which these institutions are located as follows: Clinton, Ulster, Wayne, and Westchester, 1 each; Seneca, 2; Erie, Monroe, and Onondaga, 3 each; Suffolk, 4; Oneida and Rockland, 5 each.

† Figures in this column include residents of foreign countries as follows: Albany, Greene, Herkimer, Rockland, and Suffolk, 1 each; Erie, Essex, Saratoga, and Sullivan, 2 each; Franklin, 5.

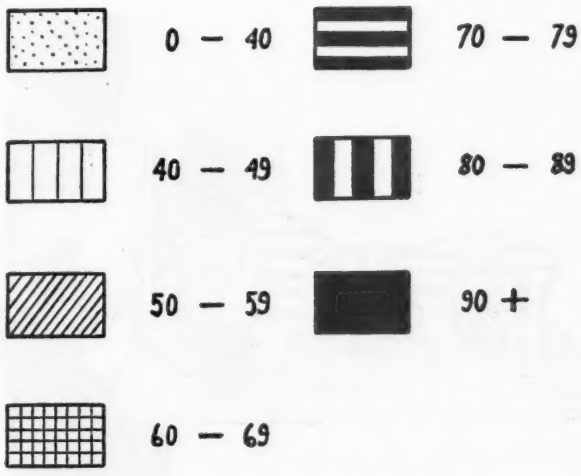
Maps 1 and 2 picture the recorded and resident death-rates in the urban areas of the several counties. Maps 3 and 4 show the corresponding facts for the rural areas of counties, map 5 presents the resident death-rates in the total areas of counties, and map 6 pictures, in juxtaposition, the resident death-rates of the urban and rural parts of each county. The various types of shading in each of these maps represent the same range of rates. This was done to simplify the interpretation at the sacrifice of the accentuation of several high points. The solid black shading, for example, represents rates in excess of 90 per 100,000 population. This shading, therefore, stands equally for a rate of 91 and a rate of 1334.9. Whenever occasion warrants we shall call attention, in our discussion, to exceptional rates.

DEATH-RATES OF URBAN AREAS (TABLE 4 AND MAPS 1 AND 2)

The allocation of deaths in cities with a population of 50,000 and over, according to residence, reduces the rate of Buffalo from 94.5 to 85.0 and the rate of Albany from 119.6 to 110.3. The resident rates of the other cities in this population group are higher than the recorded rates.

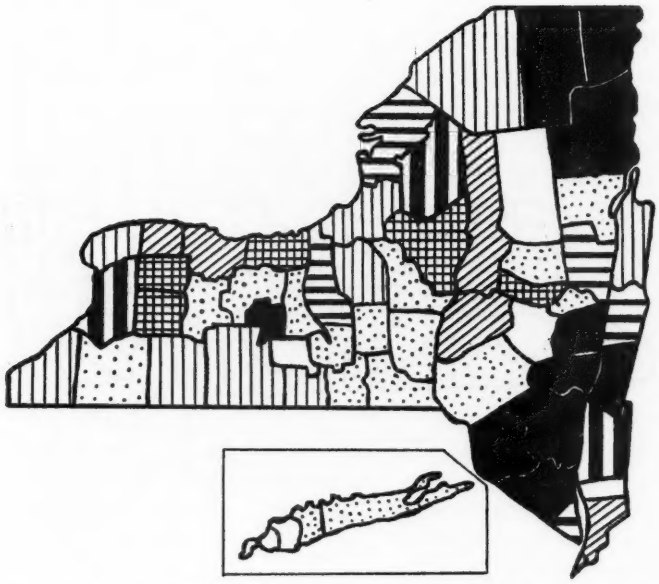
The resident rate of the group of cities of 25,000–50,000 population (75.4) is but slightly higher than the recorded rate (72.8). The difference in the recorded and resident rates in the next group of places, 10,000–25,000, is considerable, the resident rate (73.8) being 52 per cent higher than the recorded rate (48.5). In the group of smallest incorporated places, 2,500–10,000, the resident rate (69.1) is 27 per cent below the recorded rate (94.1). This group of places is, in general, more of a rural than an urban nature, and shares with the rural area the characteristic of having a large number of nonresident sufferers from tuberculosis. The number of deaths recorded in this group was 535, of which 210 were residents of the communities in which the death occurred, 13 residents of the rest of the county, 234 residents of other parts of the State, and 78 residents of other States. On the other hand, 183 residents of these small communities died in other places in the State, making the total number of resident deaths 393. In short, the resident death-rates of most of the urban communities, except the smallest, are higher than the recorded rates.

We have also computed by counties the rates of mortality in urban areas, including all incorporated places with a population of 2,500 and over. Space does not permit us to present these figures in detail, but the general situation is shown pictorially in maps 1 and 2.

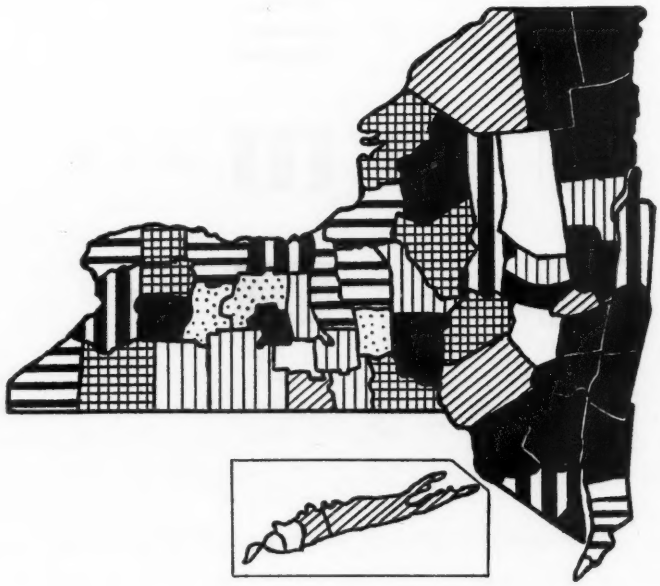


KEY TO MAPS 1 TO 6

Death-rates for tuberculosis, all forms, per 100,000 population



MAP 1. Recorded death-rates from tuberculosis, all forms, per 100,000 population, in urban areas of counties.



MAP 2. Resident death-rates from tuberculosis, all forms, per 100,000 population, in urban areas of counties.

Four counties, Hamilton, Putnam, Schoharie and Schuyler, are not shaded, the first two being wholly rural and the last two having no deaths from tuberculosis in 1926. The picture of the resident rates is, in general, darker than that of the recorded rates. The striking difference between the recorded and resident death-rates of the three resort counties (Essex, Franklin and Sullivan) is sacrificed to the choice of a uniform set of shading in which the darkest shade represents rates of 90 and over.

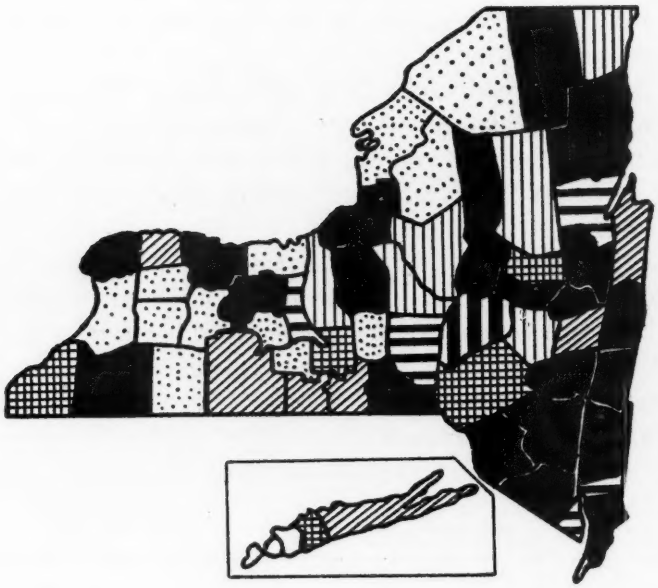
The recorded deaths in the urban area of Essex County numbered 71, in Franklin County 148, and in Sullivan County 93, the resident deaths being 7, 17, and 13 respectively. The recorded death-rates were almost of astronomical magnitude—Essex County with a rate of 1201.6, Franklin County 851.5, and Sullivan County 1334.9, the resident death-rates being 118.5, 97.8, and 186.6.

We list below all counties in which the resident or recorded rates of the urban areas were in excess of 100:

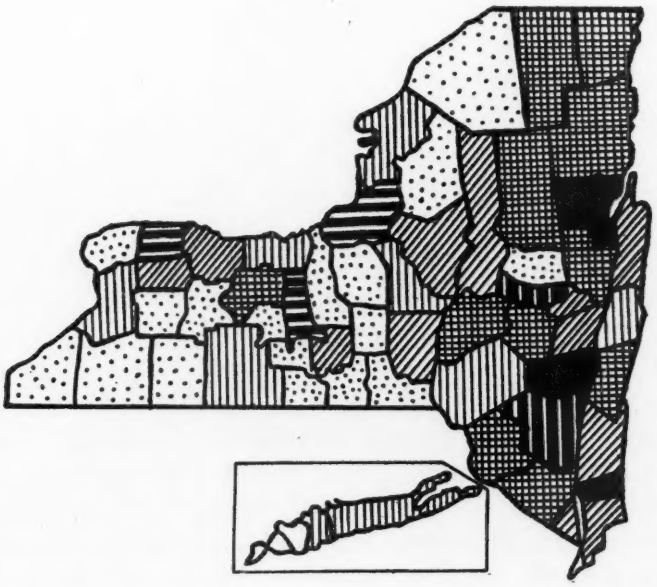
COUNTY	RATES	
	Recorded	Resident
Albany	97.6	103.2
Chenango	23.9	107.7
Clinton	137.0	111.3
Columbia	114.5	149.7
Dutchess	84.1	114.1
Essex	1,201.6	118.5
Franklin	851.5	97.8
Greene	110.6	202.8
Lewis	86.0	114.7
Rensselaer	77.7	121.5
Sullivan	1,334.9	186.6
Ulster	138.9	116.6
Yates	91.1	127.6

DEATH-RATES OF RURAL AREAS OF COUNTIES (TABLE 5 AND MAPS 3 AND 4)

The recorded rates of the rural areas of counties ranged from a minimum of 8.1 in Yates to a maximum of 306.1 in Dutchess County. Eighteen counties had rates in excess of 100. The resident death-rates ranged from the same minimum of 8.1 in Yates County to a maximum of 103.3 in Warren. In this list of counties there was but one (Warren) with a resident rate in excess of 100. Two counties had rates between 90 and



MAP 3. Recorded death-rates from tuberculosis, all forms, per 100,000 population, in rural areas of counties.



MAP 4. Resident death-rates from tuberculosis, all forms, per 100,000 population, in rural areas of counties.

100, two between 80 and 90, three between 70 and 80, eleven between 60 and 70, twelve between 50 and 60, and twenty-six counties had rates below 50.

In thirty-six counties the resident rates were lower than the recorded rates, in eighteen counties they were higher.

The increase in the resident death-rates was based on more than ten deaths in but one county (Erie), the recorded deaths numbering 32 and the resident deaths 47, the corresponding rates being 33.7 and 49.5. In all other counties, whose resident death-rates were higher than the recorded rates, the increase was less than ten deaths. In Hamilton County, for example, the resident death-rate was higher by one-half, this increase however, represented but one death. Similarly, the increase in the resident rate of Schuyler County was based on only one death. Decreases in the death-rates were most marked in the following counties:

COUNTY	DEATHS		RATES	
	Recorded	Resident	Recorded	Resident
Broome	45	13	116.8	33.7
Cattaraugus	49	16	119.9	39.2
Dutchess	139	27	306.1	59.5
Franklin	84	20	289.6	68.9
Monroe	102	34	157.5	52.5
Niagara	41	11	128.7	34.5
Onondaga	67	24	101.0	36.2
Rensselaer	57	14	186.1	45.7
Saratoga	45	21	144.8	67.6
Schenectady	34	11	181.1	58.6
Sullivan	77	22	222.3	63.5
Westchester	92	34	139.1	51.4

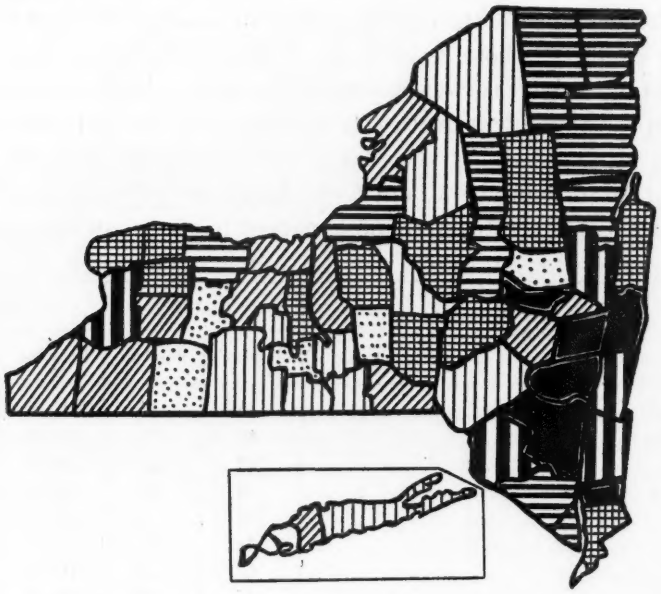
Pictorially, the disparity between the recorded and resident rates is quite striking. In map 3 twenty-one counties are shown in solid black with rates of 90 or over. In map 4 only three counties appear with rates in excess of 90, namely, Greene (94.6), Putnam (93.5), and Warren (103.3).

DEATH-RATES OF TOTAL AREAS OF COUNTIES (TABLE 6 AND MAP 5)

The recorded death-rates in the total areas of counties ranged from 14.8 in Schuyler to 500.1 in Franklin. Rates in excess of 100 were recorded in thirteen counties. Of these, the rates in nine counties ranged

between 100 and 200, Dutchess County had a rate of 249.9, Essex 320.9, Sullivan 408.7, and Franklin 500.1.

The list of resident rates shows only two counties with rates in excess of 100, namely, Rensselaer (102.1) and Greene (115.0). In a majority of the counties (thirty-two) resident rates were lower than the recorded rates, in one county (Chautauqua) the two rates were identical (56.6),



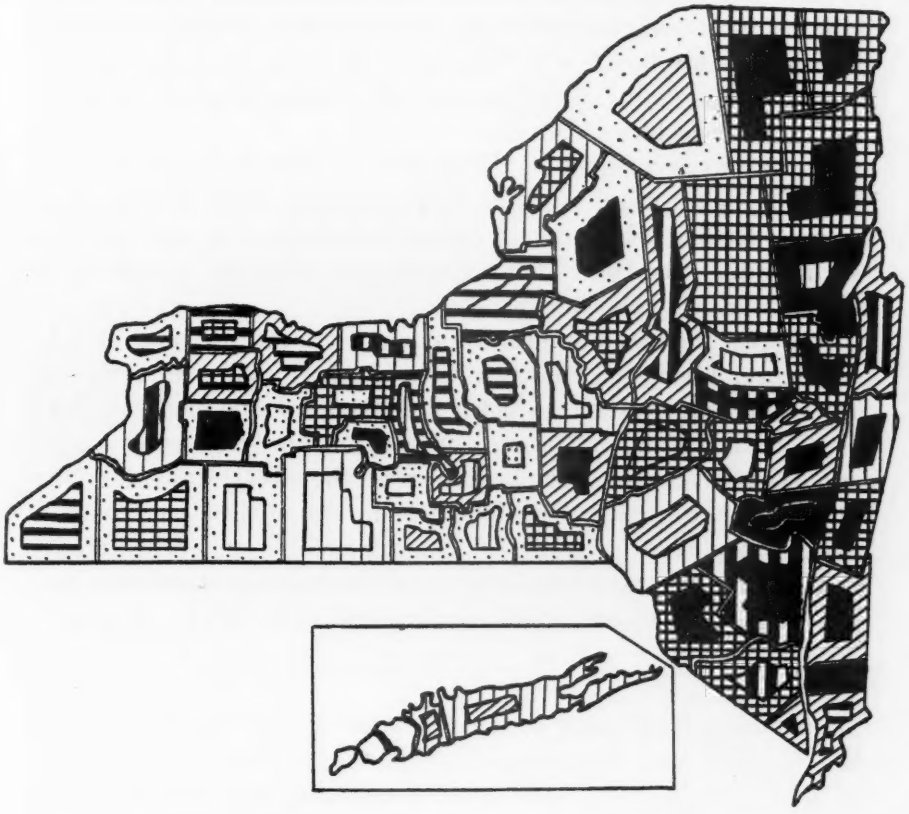
MAP 5. Resident death-rates from tuberculosis, all forms, per 100,000 population, in total areas of counties.

and in twenty-four counties (most of them with a considerable urban population) the resident rates were higher than the recorded rates. The allocation of deaths according to residence had the greatest effect, of course, upon the rates of the three leading resort counties, as follows:

	RECORDED	RESIDENT
Essex	320.9	78.6
Franklin	500.1	79.8
Sullivan	408.7	84.1

It is interesting to note that even when all deaths of nonresidents are deducted the rates of these counties remain comparatively high. Ar-

ranging the resident rates in descending order of magnitude we find that Sullivan County is ninth from the top, Franklin twelfth, and Essex thirteenth. In interpreting these figures we must, however, bear in mind the fact that our computations are based on information contained in the death certificates, which is not mathematically accurate. If we knew



MAP 6. Resident death-rates from tuberculosis, all forms, per 100,000 population, in urban and rural areas of counties. The inner shading of each county represents its urban, the outer shading its rural rate.

more about the past history of the 35 persons who were, according to our best present knowledge, residents of Sullivan County, the total of resident deaths might be reduced still further with a corresponding reduction in the death-rate. In other words, the resident death-rates of the resort counties, as well as the other counties of the State, are simply a closer approach to reality than are the recorded rates.

To illustrate the process by which the resident death-rates were ob-

tained, let us consider in greater detail the facts regarding some definite county, for example, Dutchess. Deaths from tuberculosis recorded in that county in 1926 numbered 251, of which 81 were residents of the county; 3 residents of the county died elsewhere, making a total of 84 resident deaths. Of the nonresidents who died in Dutchess County, 145 came from other parts of the State, and 25 from other States. Most of the deaths of nonresidents occurred in the several institutions located within the county limits: 6 in Matteawan Hospital, 60 in the Hudson River State Hospital, 2 in the Harlem Valley State Hospital, and 80 in the U. S. Veterans Bureau Hospital.

Map 6 shows in combination the resident urban and rural death-rates in the fifty-seven counties of the State, exclusive of New York City. The inner shading of each county represents its urban, the outer shading its rural rate. The two counties Putnam and Hamilton are shown in solid shading, being wholly rural.

Comparing the urban and rural resident death-rates we note that in one county, Livingston, the two were identical (36.7), in forty-five counties the urban rates were higher than the rural, and in eleven counties (Cortland, Madison, Ontario, Orleans, Otsego, Schenectady, Schoharie, Schuyler, Seneca, Tompkins, Warren) the reverse was true. The last fact is of no particular significance, only two of the eleven counties having a population over 50,000 (Ontario, 55,758 and Schenectady, 118,178) and their rural and urban rates are based on small numbers. The counties with a large population show invariably high urban rates.

CONCLUSION

In summing the various statements made in the preceding pages I want to stress once more the point that the resident death-rates are not presented as exact expressions of mortality from tuberculosis in *individual* cities and counties of the State. In most instances these rates are merely better approximations to actuality than are the recorded rates. But one important fact, I hope, has been established by the facts brought together in this paper, namely that *the resident death-rate from tuberculosis of rural New York is lower than the urban rate.* This relation between the rural and urban rates is certainly not peculiar to the year 1926; a similar analysis of the figures for the immediately preceding years would, without doubt, lead to the same general result, because observations based on the experience of more than five million people are not subject to violent fluctuations.

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